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ENHANCED ANION TRANSPORT USING SOME EXPANDED PORPHYRINS AS CARRIERS

ENHANCED ANION TRANSPORT USING SOME EXPANDED PORPHYRINS AS CARRIERS

by

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Chapter 1

Introduction

Supramolecular chemistry involves the association of two or more chemical species through intermolecular interactions.[1] The two components of a supermolecule have been named receptor and substrate, respectively. The receptor either natural or synthetic, is usually a large molecule that is able to bind a smaller chemical species. The substrate is the specie whose binding is being sought. It can be neutral as well as charged, such as a metal or an organic cation or an inorganic or organic anion. The geometry of both the initial, uncomplexed receptor and the final receptor-substrate complex can be spherical, tetrahedral, and/or linear. The receptor is said to be capable of effecting molecular recognition when it is able to bind, by virtue of its design, a specific substrate or set of substrates. Recognition is also the key first step that allows certain molecular receptors to serve as catalysts and/or carriers.

As a molecular reagent or catalyst, the receptor, bearing reactive functional groups, can perform chemical transformations on a bound substrate. Hydrogen transfer[2] and ester cleavage[3] reactions by such receptors are among the most common that have been investigated using receptor based, enzyme-like model studies.

As a carrier, the receptor acts as a vehicle by which a substrate can be translocated or transported. It is this latter process, particularly anion transport, that is the primary concern of this thesis. Since, as will become clearer from later chapters, anion transport depends on the

selectivity of the receptor and the stability of the anion-receptor complex, a few of the known anion receptors are now discussed briefly in the paragraphs below.

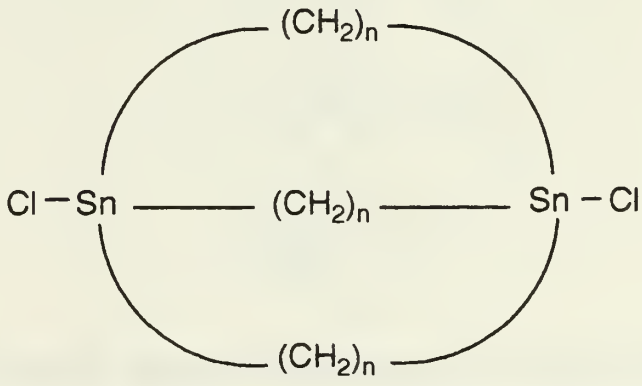
Anion-receptors.

Anion binding by an organic ligand has been less explored than cation chelation, despite its importance in chemical and biological processes.[4] Several examples of anion-receptors can be found in nature. Two such examples are the natural polyamines and certain naturally occurring metallo-enzymes. Natural polyamines like putaccin, spermidine, and spermine[5] are known to bind nucleotides. Biological metallo-enzymes, such as the Zn^{2+} containing carboxypeptidase A, specifically recognize and bind anionic guest species via so-called "ligand-protein-central metal cation-guest anion" ternary interactions.[6]

To date, non-biological, synthetically made polyammonium macrocycles and macropolycycles have been studied most extensively as synthetic anion-receptors. They bind a variety of anionic species such as inorganic anions, carboxylates, and phosphates[1] with a high degree of stability and selectivity. Strong and selective complexes of the spherical halide anions have been formed by several macrobicyclic and by spherical macrotricyclic polyammonium receptors.[7]

In a well-documented example of halide anion recognition by a macrobicyclic receptor, Newcomb et al. used ^{119}Sn NMR spectroscopy

to show that a macrobicyclic host containing bridgehead tin atoms can bind halides in solution.[8] They found that macrobicyclic host **1** is able to bind fluoride exclusively. Hosts **2** and **3,** on the other hand, are able to bind chloride better than host **4**, due the more suitable cavity size.

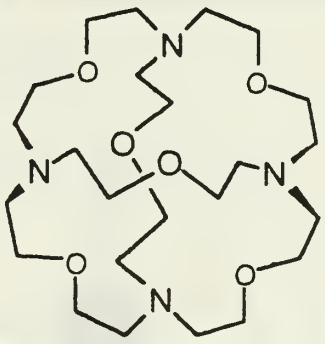


1: n = 6, **2:** n = 8, **3:** n = 10, **4:** n = 12

Dr. Jean-Marie Lehn, a leader in the area of molecular recognition and co-recipient of the 1987 Nobel Prize, has been able to characterize a number of anion-cryptate complexes formed by inclusion into the cavities of the cryptates.[9] The cavities contain anion binding sites, such as the protonated amines, and are able to form ionic hydrogen bonds, N^+--H···X^-.[10] He has reported the complexation of various halides by both macrobicyclic and macrotricyclic receptors.

In 1975, Lehn and co-workers showed that a number of protonated spherical macrotricyclic amines can form highly stable anion

cryptates with spherical halide anions.[11] They showed, for example, by using ^{13}C NMR spectroscopy that the tetra-protonated macrotricycle (**5**·H_4^{4+}) is able to form a highly stable chloride inclusion complex.



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Inclusion of F^- and Br^- was also established by ^{13}C NMR. However, neither I^-, nor any of the polyatomic anions, NO_3^-, $CF_3CO_2^-$ or ClO_4^-, were found to bind.

The stability and selectivity of the chloride complexes formed by this and other macrotricycles of similar design, were much higher than the previously reported Cl^--binding macrobicyclic systems. The results show a topological macrotricyclic cryptate effect influencing both the stability and selectivity of the anion complexes. Clearly, the high degree of stability and selectivity of a macrotricycle, is due to its closed and rigid cavity, which in turn is brought about by its high dimensionality, connectivity, and cyclic order.[10]

Iodide-cryptate complexes with macrotricyclic receptors have also been observed. In 1986, Schmidtchen et al. were able to obtain

direct proof of such an inclusion complex as the result of an X-ray crystal structure analyses of a macrotricycle-iodide complex.[12] In this case, the Iodide anion fits snugly in the molecular cavity, held by a tetrahedral array of N^+--H···X^- hydrogen bonds, as indicated schematically below (Figure 1.1):

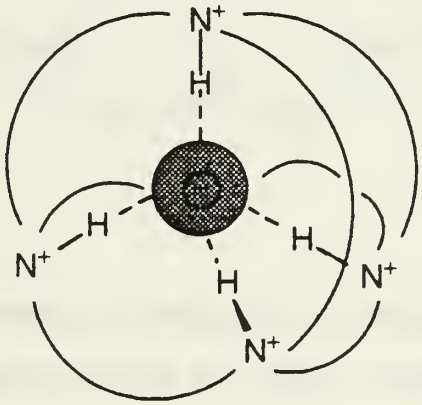
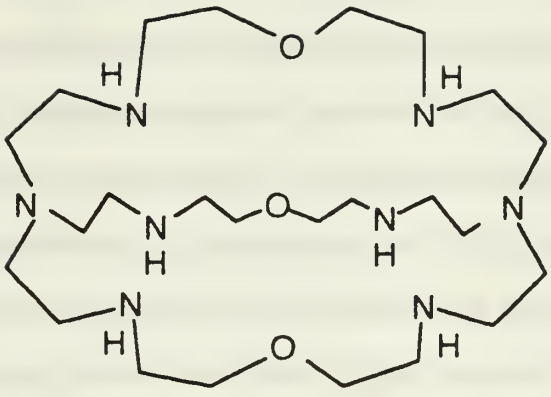


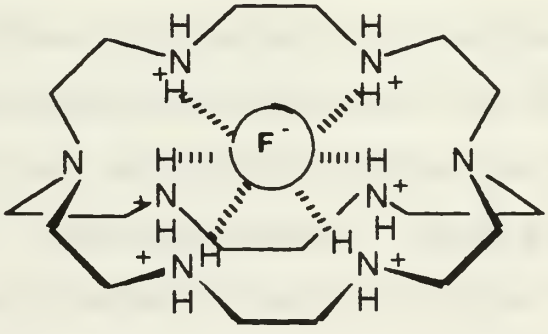
Figure 1.1. A schematic diagram of a spherical macrotricycle binding a substrate in a tetrahedral array of hydrogen bonds.

In 1988, Lehn et al. were able to obtain crystal structures of three anion cryptates formed by the hexa-protonated macrobicyclic receptor, bis-tren **6**-6H^+ with F^-, Cl^-, and Br^-.[13] The small F^- ion is tetra-coordinated, while Cl^- and Br^- are bound in an octahedron of hydrogen bonds. Although binding was achieved, ligand distortion occurs due to the non-complementarity between these spherical anions and the ellipsoidal cavity of **6**-6H^+. The cavity of the bis-tren receptor is best suited for the linear triatomic substrate, N_3^-.[14]



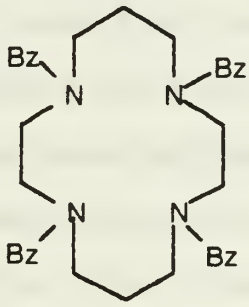
6

Another, more recent example of a F^- binding macrobicyclic receptor was reported by Lehn et al. in 1989. They were able to synthesize an octaaza macrobicyclic polyamine that can form a fluoride cryptate in which the F^- substrate is hexacoordinated to the ligand.[15] X-ray crystallography confirmed the quasi-trigonal prismatic geometry of the resulting complex (**7**).



7

Recent studies of macromonocyclic polyamines such as **8** and **9**, have revealed reactivities with many biological polyanions, such as polycarboxylates, phosphate anions, catecholamines, and other biologically relevant compounds.[16] Polycarboxylates, in particular, can bind to these polyammonium macrocycles with high stability and selectivity. A strong complex is formed when the polycarboxylate interacts with several ammonium sites of the macromonocycle.



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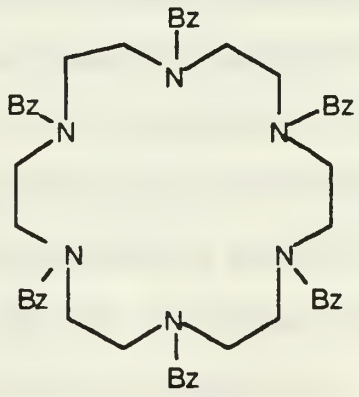
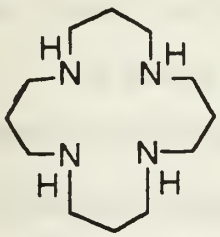


9

Prof. Eiichi Kimura and co-workers discovered that certain macrocyclic polyammonium cations with more than one proton within their cavities, have rigid cyclic conformations due to intramolecular N^{+}-H ···N hydrogen bonding.[17] Simply speaking, these polyamines behave as "polycations" due to the number of protons present in a condensed, narrow space. As "polycations" they may

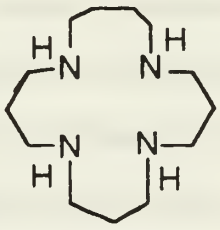
hydrogen bond with oxyanions, forming ion pairs.

This discovery of ion-pair formation between macromonocyclic polyamines and certain polycarboxylates was made in 1981 as the result of electrophoretic studies being carried out in Kimura laboratories.[18] Specific polycarboxylates used as buffers were found to influence strongly the sequence and migration distances of some polyamines. It was observed that in monocarboxylate buffers, such as acetate and lactate (pH6), all the polyamines tested, migrated as anticipated. That is, they moved as protonated cations toward the cathode at more or less similar rates. But in a citrate buffer, at the same pH, the larger macrocyclic polyamines showed slow movement or migration toward anode, while the small polyamines showed no movement at all. Thus, polyamines (**10**)-(**15**), all migrated, while smaller macrocyclic triamines, such as the cyclic spermidines, and tetramines, (**16**)-(**19**) were virtually unaffected.



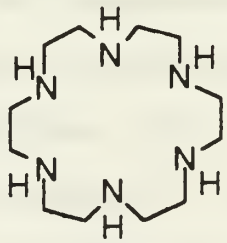
[16] ane N_4

10



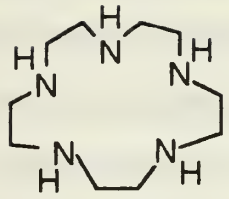
[17] ane N_4
(cyclic spermine)

11



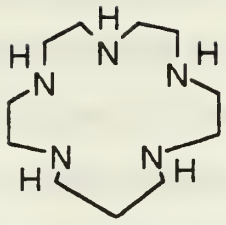
[18] ane N_6

12



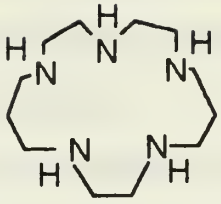
[15] ane N_5

13



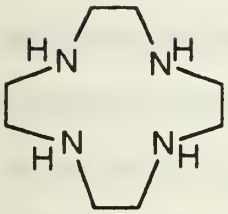
[16] ane N_5

14



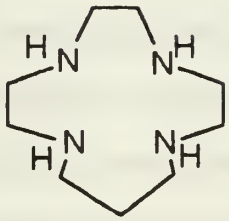
[17] ane N_5

15



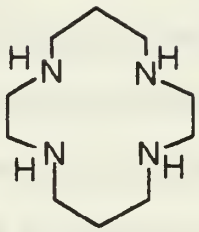
[12] ane N_4
(cyclen)

16



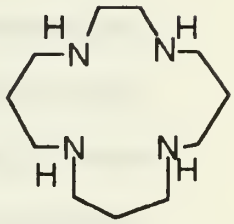
[13] ane N_4

17



[14] ane N_4

18



[15] ane N_4

19

Similar observations were made when other polycarboxylate buffers, like malate, malonate, maleate, succinate, and fumarate were used.

The above findings led to the proposal of ion-pair formation between certain macrocyclic polyamine polycations, H_3L^{3+} or H_4L^{4+}, and certain polycarboxylate anions (here, L= (**10**)-(**15**)).[17] At about pH 7, for example, the larger polyamines can accommodate three or more nitrogen-bound protons and, therefore, could possibly form a 1:1 ion-pair complex with say, citrate. The smaller polyamines, at the same pH,

can accommodate only two nitrogen-bound protons. Apparently, as dications, these polyamines are unable to provide sufficient electrostatic attraction to polycarboxylate anions for ion-pair formation.

Taken together, the studies summarized above provide some insight into what factors contribute to the stability of anion-ligand complexes. First, for a given receptor molecule, the anions most strongly complexed are usually the smallest ones and/or those bearing the highest charge. Second, the greater complex stability and selectivity attained with certain macrocyclic ligands can generally be attributed to the formation of closed and relatively inflexible complex structures (i.e. acyclic vs. monocyclic vs. bicyclic etc.) Finally, in these cases where electrostatic interactions play a major role in regulating anion binding, the higher the polyammonium cation charge, the stronger is the affinity for anions.

Biological Transport Systems.

Many biological processes are dependent on either the presence or the absence of certain metabolites at any given time.[19] Facilitated transport is one of at least four possible types of processes by which the passage of metabolites through a biomembrane can occur. The other three processes are: (1) Mass flow through pores; (2) passive diffusion, and (3) through pinocytosis.[20] One of the first biological transport systems to be studied in detail involves the regulation of K^+ and Na^+ inside animal cells.[19] Both cations are transported unidirectionally against a concentration gradient. The transmembrane protein responsible for the flux is Na^+-K^+ ATPase. Other ion-translocating ATPases exist for H^+, Na^+, and K^+ and Ca^{2+}.[21] Some other well-studied biological transport systems are the lactose transport in *E. coli* and other bacteria; glucose transport in most animal cells; HCO_3^-/Cl^- anion channel in erythrocytes; and the so-called ATP/ADP exchanger.[19]

A breakdown in the mediated transport of an essential metabolites can be detrimental. For example, the chloride channels in epithetial cells are mediated by a regulatory protein called the cystic fibrosis transmembrane conductance regulator (CFTR). A mutation in the gene for CFTR leads to abnormal Cl^- transport, which, it is currently thought can lead to cystic fibrosis.[22]

Theory of Membrane Transport.

A form of facilitated diffusion is carrier or receptor-mediated transport. This involves the transfer of a substrate across a membrane, facilitated by a receptor molecule. Membrane permeability by a substrate may be induced by a receptor molecule via a four step cyclic process. The four steps are 1) association, 2) forward diffusion, 3) dissociation, and 4) back diffusion (Figure 1.2).[23]

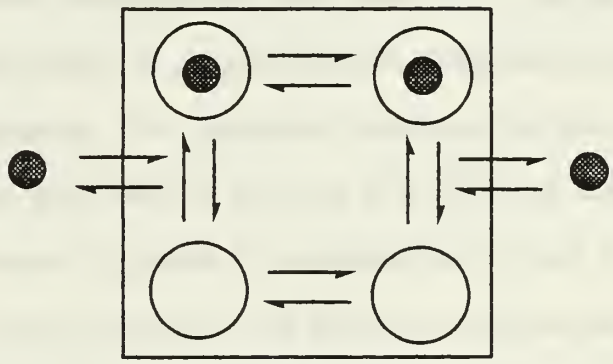


Figure 1.2. Schematic representation of carrier-mediated transport through a membrane. Closed circles represent substrates; open circles represent carriers; and closed circles within open circles represent complexes.

Facilitated diffusion (transport) differs greatly from passive or simple diffusion. Simple diffusion occurs when the substrate is soluble in the liquid membrane and can diffuse freely across it. Facilitated diffusion implies "picking up" a substance at the point of high supply and delivering it at the point of demand. The use of a carrier molecule usually accelerates transfer of a substrate down a concentration gradient. Facilitated diffusion can be distinguished from passive diffusion by kinetic measurements and specificity. Simple diffusion shows a linear increase of velocity with an increasing concentration of the diffusing substrate. The kinetics of mediated transport by a carrier molecule, on the other hand is like that of an enzyme-catalyzed reaction.[24] The rate of uptake of a substrate into a cell, for example, which initially has no substrate, is at first linear with respect to time. Eventually, the rate of net uptake decreases to zero, and a steady state exists in which equilibrium is obtained (i.e. the rate of influx equals the rate of efflux).

Passive diffusion can be best illustrated mathematically by Fick's law which states that the rate of diffusion of a dissolved substance along a column of fluid is proportional to the concentration gradient. The following equation describes this rate of transfer of the substrate via diffusion:[24]

$$v \propto [S] - [S'] / L$$

where v = velocity of transfer,

S = substrate concentration in one direction,

S' = substrate concentration in the opposite direction.

L = thickness of membrane

Competitive inhibition studies can be important tools by which passive diffusion can be distinguished from facilitated diffusion. Inhibition by substrate analogs or other suitable substrates would not be expected if simple diffusion is occurring, but is expected for carrier-mediated transport.

Numerous factors can alter rate of transfer of a substrate across a membrane. Here are some of the major factors that can influence rate:

(a) Temperature. This, alters the rate of random movement of molecules.

(b) Solvent flow in the membrane either with or against the direction of the net substrate transfer; i.e., solvent drag will greatly affect rate. This is a variation on viscosity affects.

(c) Relative solubility of solute molecules in the solvent on either side of the liquid membrane and in the membrane itself.

In terms of designing experiments that are reproducible and easy to interpret, the desire is to try to minimize the influence of or at least

changes in the above factors. This can be done via physical means or by designing an experimental system in which these factors can be assumed to be constant and hence safely incorporated into a single constant called the diffusion coefficient, D. Here, D would represent the rate of movement (i.e. mass per unit area of membrane per unit time) times the membrane thickness per unit of concentration difference and would be expressed in the following form:[24]

$$v = D [S] - [S'] / L$$

thus,

$$D = v \cdot L / [S] - [S']$$

The relationship between the one-way rate (v) of diffusion of molecules across a boundary and the concentration of the molecules in the compartment from whence they are diffusing is simplified to the following:

$$v \propto D[S]/ L$$

where D is the slope of the linear relationship.

Carrier molecules which can transport a substance across or through a liquid membrane can be looked at as being mobile

absorption sites. In order to evolve a kinetic model for carrier transport, we need to make the following assumptions:[24]

1) Equal number of carrier molecules move through the membrane in each direction and they do so at equal rates.

2) The total number of carrier molecules at each surface does not change.

3) The carrier molecule stays long enough at the source phase to establish an equilibrium with the substrate before moving to the receiving phase.

4) The substrate is being continually removed from the source phase, thus a steady state or equilibrium develops.

5) The substrate is present on one side only initially and over a period of observation, the concentration on the other side increases.

The assumptions listed above meet the criteria for treatment using a modified Michaelis- Menten model for enzyme kinetics.[24] In other words, the terms and the equation used in this classic theory can be adopted for use in modern transport kinetics. Here, the key, classic Michaelis-Menten equation is:

$$v = \frac{Vmax[S]}{[S] + Km}$$

Now, redefining the above terms for transport kinetics, v becomes the transport rate. The value of v will depend on the concentration of the carrier, the number of substrate molecules that can be transported per carrier and the rate of turnover of the carrier. The term V_{max} represents the maximal rate of transport. This value will depend on the maximum number of substrate molecules available for transport, and the proportion of the maximum number that will dissociate at the opposite surface. The term K_m is defined as the concentration of substrate at which the transport rate is exactly half the maximal transport rate, V_{max}. The K_m variable is sometimes referred to as the affinity (i.e. the tendency to associate) for the carrier-substrate complex. Low values of K_m have been considered as reflecting a high affinity of the substrate for the carrier; conversely, high K_m values have been correlated with low substrate-carrier affinity.[24]

When diffusion contributes to the transfer of the substrate, the total rate of transfer can be expressed as the sum of these two transfer modes :

$$v = \frac{V_{max}[S]}{[S] + K_m} + \frac{D[S]}{L}$$

The Michaelis-Menten treatment is the simplest of those models that describe simple carrier-mediated transport phenomena. More complicated and conclusive models have also been developed.[25] These, however, will not be reviewed here.

Basic Principle of Bulk Liquid Membrane Transport.

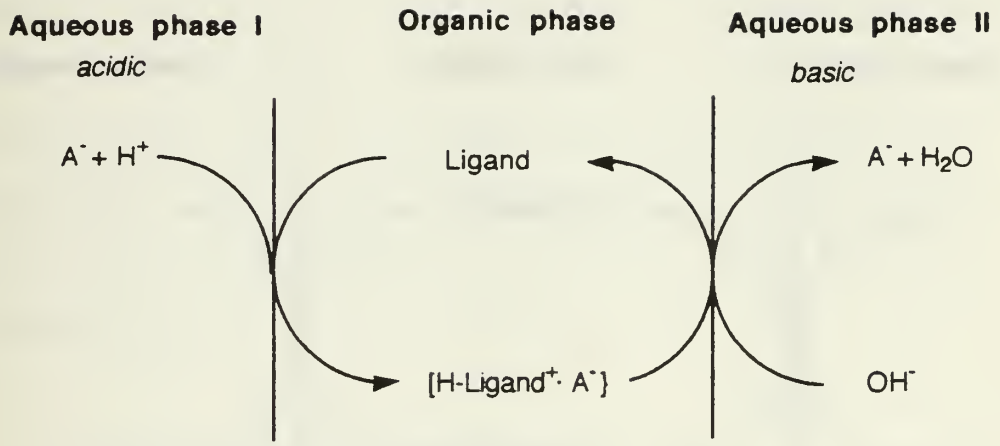
The basic principle of liquid membrane transport is quite simple. The anion or cation first reacts with the carrier to form a complex which is soluble in the membrane, but not in the adjacent solutions. After diffusion across the membrane, this complex dissociates to regenerate the free carrier and the original anion or cation. Selective transport occurs when the carrier binds and/or releases a substrate with partial or complete specificity. The rates for complex formation and dissociation are usually faster than diffusion through the membrane.

A typical liquid membrane experiment consists of dissolving the carrier in an organic matrix which forms a thin layer between two aqueous solutions containing different substrate concentrations. The liquid membrane experiments are typically performed in a U-shaped glass tube apparatus and this membrane system is called "bulk liquid membrane."[26] A lipophilic carrier dissolved in CH_2Cl_2, $CHCl_3$, or another organic media is placed in the bottom of the U-tube. Two aqueous phases (Aq. I and Aq. II), referred to as the source and

receiving phases, respectively, are placed in the arms of the U-tube, floating on the organic membrane phase. The membrane phase is constantly stirred by a magnetic stirrer. The quantity of the substrate transported determined as a function of time using appropriate physical methods.

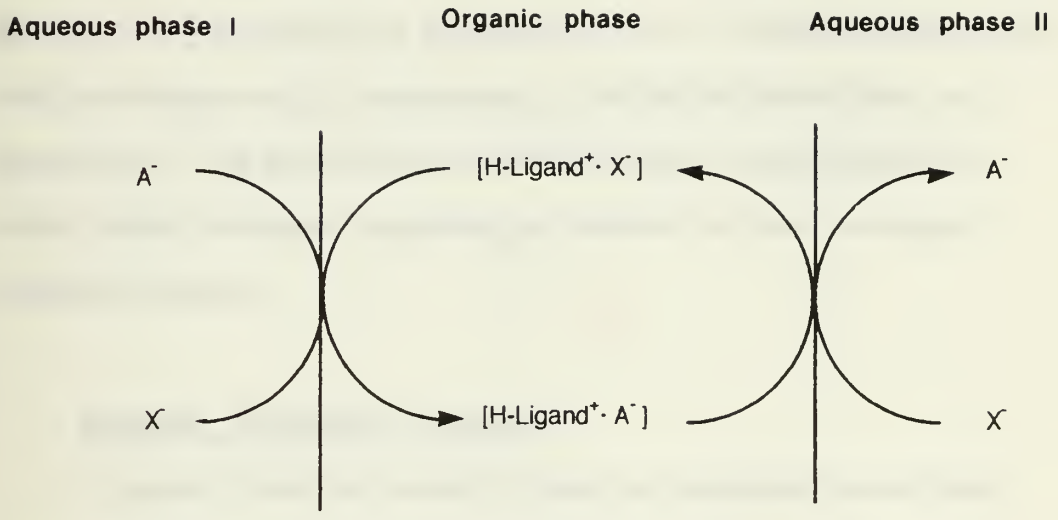
The term *symport* is defined as the simultaneous transport of two ions in one direction (Scheme 1.1). Symport transport usually involves a guest anion and cotransported cation (such as a proton) co-complexed with a common neutral carrier, which itself is soluble in the membrane phase. Once the complex diffuses across the membrane, it dissociates at the membrane interface of Aq. II. The guest anion and cation are thus carried in the same direction. If the cotransported cation is a proton, an initial proton concentration gradient, established between Aq. I and Aq. II, can serve to drive the transport. At the more basic side of the interface, deprotonation enforces the release of a guest species such as HX. The net result is effective anion transport for, in this instance, X^-.

Scheme 1.1



Antiport is when the movement of an ion in one direction drives the movement of a second ion in the opposite direction; here, too, one concentration gradient is being used to create another (Scheme 1.2). In a typical transport experiment, being run under antiport conditions, a free lipophilic carrier binds the guest anion at the source, AqI/membrane interface and carries it through the membrane to the Aq. II/membrane interface.

Scheme 1.2



There, the bound guest anion is exchanged for a second anion which is transported back to Aq. I. As a result, the first anion is released into Aq. II. The second anion (from Aq. II) is then released at Aq. I after "back" transport. Here, it is important to note that the guest anion can sometimes be located outside of the cavity and transported as a simple ion-pair complex.

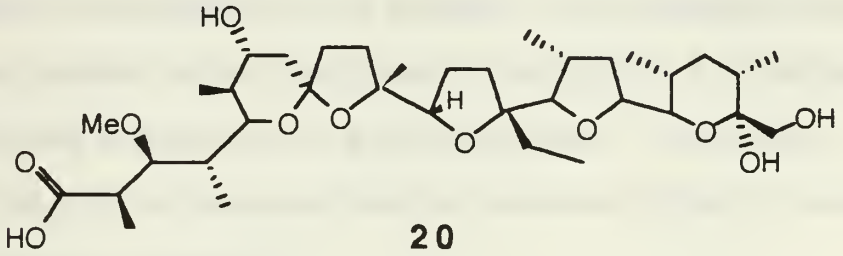
Lipophilic polyammonium macrocycles, for example, provide good carriers for both symport and antiport studies. They can bind an anion and, in many cases transport it selectively across a liquid membrane.[27] This can occur in accord with either of the scenarios outlined above, but does require "pre-protonation" at the Aq.I/

membrane interface. This protonated polyammonium macrocycle can then bind the specific anion at the Aq.I/ membrane interface and transport it through the membrane to the membrane/Aq.II interface. At this point, the bound anion is released into Aq.II. At this interface, either anion exchange and/or deprotonation of the carrier takes place, as appropriate. The driving force can thus be either proton gradient or counter anion exchange depending on whether symport or antiport conditions pertain.

Natural Transport Carriers.

In nature, there are naturally occurring biological ion-carriers known as ionophores. These, transport such ions as Na^+, K^+, and protonated catecholamines across various biomembranes. All ionophores seem to have three defining features in common. First, they all have an ability to wrap around specific cations in a three dimensional fashion. Second, they contain both hydrophilic and lipophilic portions which allow for complexation with polar substrates and solubility into organic membranes. Finally and most importantly, the complexation and decomplexation effected by ionophores must occur readily.[28] Monensin, valinomycin, and nonactin are examples of such ionophores.

Monensin (**20**) is an acyclic, polyether antibiotic that can exist in a pseudo-cyclic conformation in order to form stable complexes with metal cations (Figure 1.3).[29]



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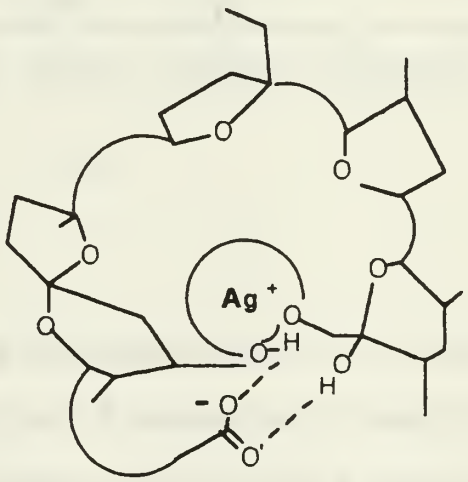
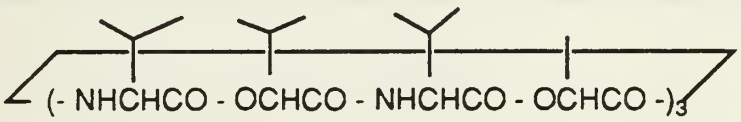


Figure 1.3. Monensin-Ag^{+}complex

Valinomycin (**21**) is produced by bacterium streptomyces.[28] It is an antibiotic with a ring structure possessing a cavity core suitable for

K^+ complexation. It has an hydrophobic exterior to allow passage through the inner mitochondrial membrane. It binds K^+ from the cytosol side of the membrane and then, the charged complex is transported to the inside of the cell where K^+ is released. The developing electrical potential gradient is the driving force for transported; it is dissipated by the pumping of protons out of the mitochondrion. The constant exchange of K^+ for protons across the membrane allows for increased consumption of oxygen.[28]



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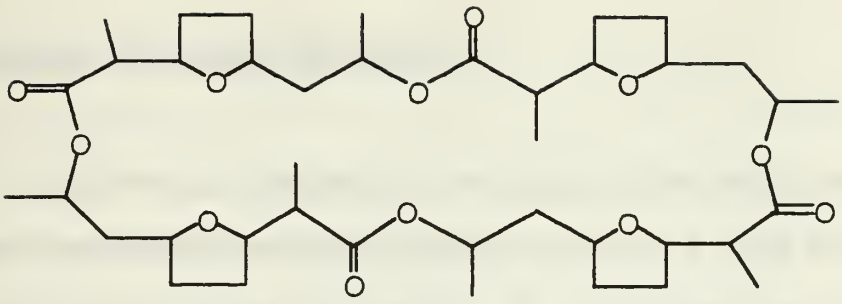
Nonactin (**22**) is also specific for K^+ ion. It has a 32-membered ring. Although the ring size is apparently too large to bind a K^+ ion strongly, the donor oxygen atoms are able to form a three-dimensional cage which accommodates the ion well.[27]



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Although ionophores form complexes with ions by wrapping around them, they still show unique selectivity and stability. Therefore, the ionophore can serve as a model for synthetic carriers.

Synthetic Transport Carriers.

Like molecular recognition, the design of innovative synthetic carriers and artificial transport systems represents a major area of research in supramolecular chemistry. [30] It is essential that certain factors be considered when designing or choosing an ion transport carrier. These factors are as followings:

(a) Complementary between size and shape of guest and carrier.

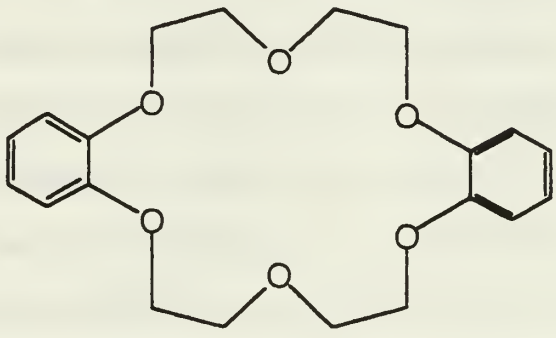
(b) Suitable ion-binding interactions.

(c) Appropriate accommodation of guest coordination geometry.

As stated earlier, transport carriers are molecular receptors with different degrees of stability and selectivity, depending on the receptor-substrate complex. Thus, transport rates and selectivity for a variety of cations and anions can be varied by modifying the structure of the receptor.

The very first liquid membrane transport study involving synthetic carriers was reported in 1973 by Reusch et al.[31] These workers used cyclic polyethers a carriers to facilitate transport of a variety of cations, such as Li^+, Na^+, Ag^+, K^+, Rb^+, and Cs^+. The high degree of selectivity observed was thought to reflect the solubility of the salt in the organic

membrane and the stability of the salt-polyether complex. In this study, the most effective carrier found proved to be the cyclic polyether dibenzo-18-crown-6 (2,3,11,12-dibenzo-1,4,10,13,16-hexaoxocyclooctadeca-2,11-diene (**23**)).



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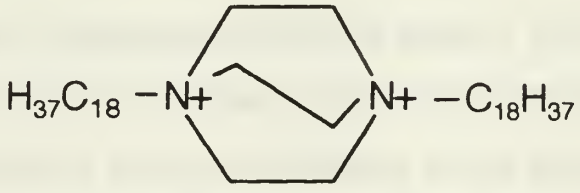
Reusch suggested a 4-step mechanism for the polyether facilitated transport, in which the following occur:[31] 1) Complexation of a specific cation by the polyether and formation of an ion pair [carrier+anion+polyether] complex, 2) diffusion of the carrier complex across the membrane, 3) release of the ions at the other side, (driven by the low concentration); then 4) diffusion of the polyether back across the membrane. Reusch proposed that the cation fits into the hole in the polyether and is stabilized by the highly electronegative oxygen environment. The linearity of transport flux vs. polyether concentration indicated the formation of a 1:1 complex.

Although there are a large number of synthetic cation transport carriers,[32] there are only a few synthetic anion transport carriers known to date. These are reviewed below.

In early work, Tabushi et al. reported a prototypical example of an anion carrier, namely a lipophilic dicationic derivative of diazabicyclooctane (**24**).[33] This compound, has two cationic centers spaced apart yet embedded in a rigid bicyclic skeleton. This design feature makes this carrier complementary to vicinal ADP dianion. The ADP dianion was more effectively transported through a liquid membrane than the geminal AMP dianion. The less effective transport of AMP dianion can be explained by the the lower interaction between it and the protonated diazabicyclooctane.



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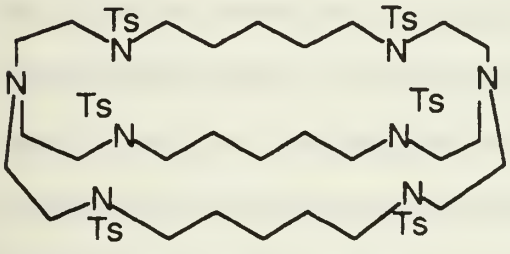
In 1988, Lehn et al. were able to show that macrobicyclic diammonium salts mediated the transport of bromide ions and protons via the formation of anion cryptates.[34] They were also able to demonstrate the effectiveness of macrobicyclic amines such as (**25**) and (**26**), for effecting the selective binding and transport of such ions

as Cl^-, Br^-, NO_3^-, and ClO_4^-. The relatively low transport rates effected by these macrobicyclic amines may be due to the inherent low selectively of such intrinsically floppy systems.



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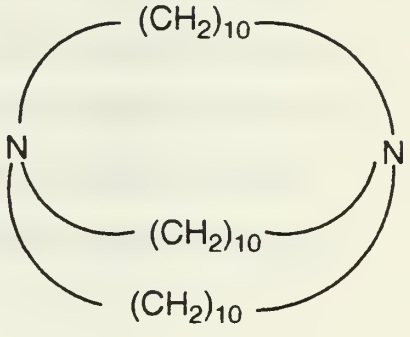

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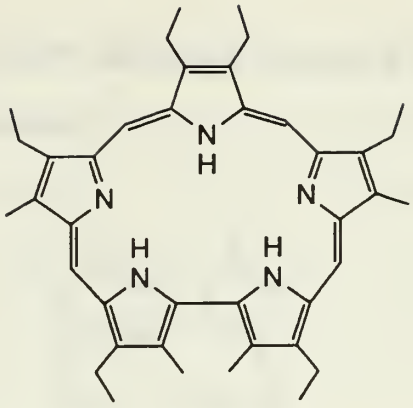
Lipophilic N-tetrabenzylcyclam (**8**, page 7) at pH 4-7, was found to be a good carrier for the through liquid membrane transport of dicarboxylate anions, such as *o*-phthalate, and of amino acid anions.[35] It was suggested that the diprotonated species, H_2L^{2+} (here L = **8**), is the active carrier species for anions.

The examples given involve facilitated transport through a bulk liquid membrane system. Other workers have investigated transport through immobilized membrane systems. Stabwiljk et al., for instance, were able to show that $KClO_4$ could be transported through a polymer

supported membrane using benzo 18-crown-6 ether.[36] Here, the liquid membrane was immobilized by making a solution of the crown ether in an organic solvent and submerging a polypropylene support (either Accurel™ or Celgard type™) into this organic solution while pulling a vacuum. He concluded that the transport of the salt through the supported membrane is a function of the diffusion rate of the cation-crown ether complex. In the membrane phase, the complex and anion exist as free ions. The diffusion of the crown ether complex was thus determined to be the rate limiting step, and it, in turn, depended on the support used and its porosity.

Sapphyrin as a Fluoride Receptor and Transport Carrier.

Sapphyrin (**27**) is a 22 π -electron expanded porphyrin that was first reported by Woodward et al in 1966.[37] Its discovery was made serendipitously in the course of an attempt to synthesize vitamin B_{12}. Free -base sapphyrin has three normal protonated pyrroles and two sp^2 hybridized nitrogens. These two nitrogen atoms are readily protonated by weak acids; thus, in the solid state, the dication complex of sapphyrin is more stable than the free base. Sapphyrin is known to form tetra-ligated metal complexes with Zn, Co and Ni.[38] Transition metal carbonyl complexes[39] and more recently, a uranyl complex[40] have also been obtained.



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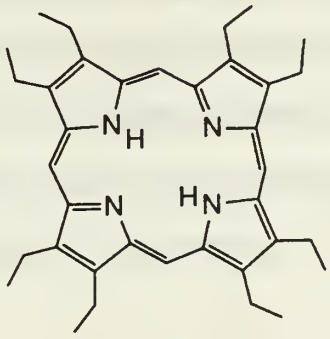
Evidence of Sapphyrin as a fluoride anion-receptor[41] in the solid state was obtained from an X-ray analysis of crystals of the mono-hexafluorophosphate salt of the diprotonated sapphyrin **27** ([**2**·(2H$^+$)·F$^-$][PF_6]).[42] The fluoride was found to be centrally located in the ca.5.5 Å diameter cavity. The X-ray structure further revealed N···F$^-$ distances ranging from 2.697(3) to 2.788(3) Å, and N-H···F$^-$ angles ranging from 167(2) to 177(3)°. The five N atoms and the central F atom were also found to be essentially planar.

On the basis of the solid state results, a question arose as to whether sapphyrin could bind fluoride anion in the solution. Fluoride transport experiments were, therefore, undertaken in an attempt to probe this issue further. These transport experiments were run under condition of a proton gradient (pH 3, pH 12) and at different pH regimes. For the sake of comparison, chloride transport studies were also conducted. Some control experiments were also conducted using octaethylporphyrin (**28**).

Octaethylporphyrin (OEP,**28**) was chosen as a control in these studies for the following reasons:



28

a) It is an 18π electron aromatic macrocycle (sapphyrin is also aromatic.)

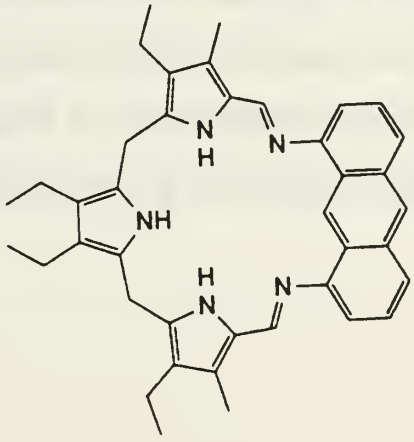
b) Although iron-porphyrin complexes are known to bind fluoride via the metal;[43] to the best of our knowledge, no fluoride inclusion complex has ever been observed with porphyrin. Intuitively, such an inclusion complex would not be possible due to the small core size (~4Å).[44]

c) Also, to the best of our knowledge, fluoride transport studies involving porphyrin as a carrier have never been reported. Again, little or no transport ability would be expected for the reason mentioned above.

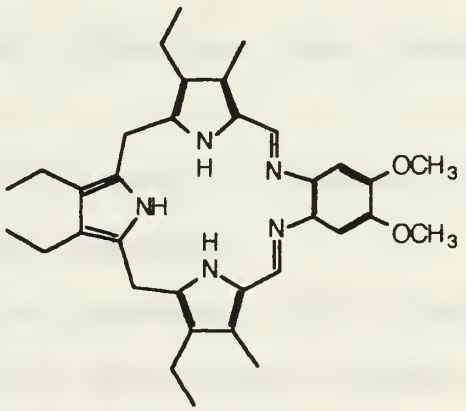
The results of the fluoride and chloride transport studies involving sapphyrin and OEP are provided in Chapter 3. This chapter represents the draft form of a paper that has been submitted for possible publication in the Journal of the Chemical Society, Chemical Communication. The author was a main contributor to this work and essentially wrote the manuscript in its entirety.

Other Possible Fluoride Receptors.

In order to explore further the possibility of enhanced fluoride or chloride transport by other possible expanded porphyrin type receptors, a non-aromatic macrocycle, anthraphyrin, was also studied. Anthraphyrin (**29**) was recently prepared and characterized by Mr. Tarak Mody in the Sessler group. An X-ray analysis of the mixed $HCl{\cdot}HBF_4$ salt of **29** revealed a chloride anion centrally encapsulated within the macrocyclic core. As with sapphyrin, this led us to consider that this material could be used for anion transport. Studies along these lines, involving F^- and Cl^-, were therefore carried out.



In these studies, summarized in Chapter 4, reduced texaphyrin (**30**), a porphyrinogen-like macrocycle reported by Sessler et al. in 1987,[45] was used as a control. As is anthraphyrin, this compound is also non-aromatic. However, it is a system with a much smaller cavity size than anthraphyrin.



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Here, it is to be noted that as is Chapter 3, Chapter 4 is in the form of a pre-publication manuscript. In this instance, submission to the Journal of American Chemical Society has already been made. However, unlike Chapter 3, the candidate was not responsible for writing up the text, just producing the transport data.

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Chapter 2

Experimental

I. U-Tube Set up:

A. General Information:

1. A U-tube apparatus is constructed of the same design as Figure A (p.52).

2. When performing fluoride transport studies, the U-tube is first coated with a Sigmacote®, and then allowed to dry for 24 hours. Sigmacote® is a special silicon solution in heptane that forms a tight, microscopically thin film on glass. It is water repellent and it helps prevent etching of the U-tube glass by HF. This coating is not necessary when performing chloride studies.

3. Buffer solutions[1] used in the antiport studies are listed below:

pH	Buffers used	Molarity
3	-Trifloroacetic acid/NaOH	0.2 M
	-Acetic acid/sodium acetate	0.2 M
5	-Acetic acid/sodium acetate	0.2 M,1.0 M
7	-Acetic acid/sodium acetate	0.2 M
	-Tris(hydroxymethyl)aminomethane-maleate	0.2 M
9	- Glycine/NaOH	0.2 M

B. Set up:

1. A clean dried U-tube is placed on a magnetic stirrer. A flat piece of cotton is placed between the U-tube and stirrer to absorb the heat generated by the stirrer. A tiny magnetic stir bar is placed in each arm of the U-tube.
2. A 10^{-3} M concentration of the carrier (either sapphyrin, anthraphyrin or OEP), in dichloromethane is made up.
3. Then,10 ml of the carrier is pipeted into the bottom of the U-tube.
4. Next, 1 ml of an aqueous solution without the anion of study, is pipeted into the arm of the U-tube designated as Aq. II. The aqueous solution is either adjusted to pH 12.0 with NaOH (if symport conditions), or buffered (if antiport conditions; see Section A).
5. Exactly, 1 ml of the Cl^- or F^- solution (diluted with either the same buffer solution in Aq. II or adjusted to a specific pH), is pipeted into the arm of the U-tube designated as Aq. I. For symport, a 0.5 M solution of HF or Cl^- (0.1 M HCl/0.4 M NaCl) is used. For antiport, a 0.25 M NaF or NaCl solution is used.
6. The membrane phase is constantly stirred by a magnetic stirrer for the duration of the experiment.

7. The amounts of either chloride or fluoride transported are then determined from its concentration in Aq. II via an ion-selective electrode.

II. Measurement of the Fluoride Anion Concentration in Aq. II Phase via an Orion Combination Fluoride Electrode:

A. General Information:

The dissociation of HF in H_2O is complicated. The total fluoride concentration, $[F_T]$, is distributed among three species in solution in the following fashion as specified by the pH: $[F_T] = [F^-] + [HF] + 2[HF_2^-]$. The formation of the aquated species HF_2^- is relatively stable. So the following equilibrium constants have to be taken into consideration in less diluted solutions: $K_1 = [H^+][F^-]/[HF]$ and $K_2 = [HF_2^-]/[HF][F^-]$.

The value of K_1 is in the range of 2.4 to 7.2×10^{-4} and that K_2 ranges from 5 to 25, depending on the method of estimation and the temperature.[2]

HF is a fairly weak acid as a solute, but a very strong acid as a solvent. As the HF/H_2O ratio increase, HF behaves more like a solvent, while H_2O acts like a strong base, consequently, the system becomes more acidic. Under these acidic conditions, HF_2^- and dimers $(HF)_2$ are formed.

At extremely low pH's and in less dilute $HF-H_2O$ solutions, protons are transferred from isolated water molecules from dimeric $(HF)_2$ species and the resulting fluoride ions, now form a stable polymeric anion complex with the dimer.[2] The ease of proton transfer is

the deciding factor at what extent this happens. The difference in solvation of fluoride ion in concentrated solutions and dilute solutions is a factor to consider in fluoride transport studies.

In order to make an accurate determination of the amount of free fluoride transported with the F^- electrode, a low-level total ionic strength adjustment buffer (TISAB) is added to all standards and samples. This buffer serves two purposes. First, it provides a constant background ionic strength. Second, as a pH 5.0 buffer, it decomplexes fluoride ions tied up as HF and HF_2 in acidic solutions and prevents erroneous potential reading in alkaline solutions due to OH^- interference. This solution has minimal fluoride background and can be used when measuring samples containing less than 0.4 ppm of fluoride. Other TISAB solutions containing complexing agents are commercially available. It must be kept in mind that these solutions can have up to 0.1 ppm of fluoride background. The low-level TISAB was prepared in the following manner:

> Deionized H_2O (500 ml) of is placed in 1L beaker. Glacial acetic acid (57 ml) and 58 g of NaCl are added. The beaker is placed in a H_2O bath and NaOH is added slowly until the pH is between 5.0-5.5. The solution is then placed volumetric flask and diluted to the mark with deionized water.

B. Measuring the free fluoride anion concentration:

1. The combination fluoride electrode was set up and its operation was checked by measuring the electrode slope in accordance with the procedure outlined in the electrode instruction manual.[3]

2. A 100 ml quantity of a 10 ppm or 10^{-3} M NaF standard solution is prepared by diluting a commercially available standard solution of 100 ppm or 0.1M NaF. 100 ml of the low-level TISAB is added to 100 ml of the 10^{-3} M or 10 ppm NaF standard.

3. Distilled water (50 ml) and 50 ml of low-level TISAB are added into a 150 ml beaker. The combination fluoride electrode is placed into the beaker.

4. Increments of the 10 ppm or 10^{-3} M NaF standard, diluted with low-level TISAB, are added to the 150 ml beaker as outlined in Table 2.1. The potential (mV) is recorded when a stable reading is displayed. A calibration curve for low-level measurements of fluoride is constructed as indicated by Figure B.

5. A calibration curve for high-level measurements of fluoride is constructed (Figure C) from potential reading resulting from serial dilutions of a 10^{-3} M NaF standard as indicated by Table 2.2.

6. A 10 μl sample is removed from Aq. II of transport experiment initially, every two hours for at least 10 hours. Each sample is diluted with 0.5 ml of deionzed H_2O and 0.5 ml of the low-level TISAB (a total volume of 1.01 ml). The potential reading of each sample is recorded. The total amount of F^-(in μmoles) transported into Aq. II is calculated by multiplying the moles of F^- found in diluted aliquot (as determined from the calibration curve) by 100.

7. The time course of fluoride transport is plotted and the initial flux is determined from the linear region of concentration vs time curve.

III. Measurement of the Chloride in Aq. II Phase via an Orion Combination Chloride Electrode:

A. General Information:

In order to make an accurate determination of the amount of free chloride with the Cl^- combination electrode, an ionic strength adjustor (ISA) is added to all standard and samples. In this case, the ISA is a 5M $NaNO_3$ solution. For low level measurements, a low level ISA is used. The low-level ISA(1.0 M $NaNO_3$) can be prepared by diluting 20 ml of ISA into 100ml of deionized H_2O.

Interference by other ions is also a major concern when using the Cl^- electrode. Here too, an excess of hydroxide ions can lead to erroneous readings. The maximum allowable ratio of OH^- molarity to the sample chloride molarity is 80:1. Hydroxide interference can be removed by acidifying to pH 4 with 1M HNO_3. The following are other interfering ions but to a lesser degree: Br^-, I^-, S^{2-}, NH_3, CN^-, and $S_2O_3^{2-}$. It should be noted that free chloride ions can form complexes with such metal ions as Bi^{3+}, Cd^{2+}, Mn^{2+}, Pb^{2+}, Sn^{2+}, and Tl^{3+}. The presence of these complexing agents will lower the measured concentration of chloride. Ways of eliminating these and other possible interferences are provided in the electrode technical manual.[4]

B. Measuring of free chloride anion concentration:

1. The combination chloride electrode was set up and its operation was checked by measuring the electrode slope in accordance with the procedure outlined in the electrode instruction manual.[4]

2. A 10^{-2} M NaCl standard solution (100 ml) is prepared by diluting a 0.1M NaCl standard solution purchased from manufacturer.

3. Deionized water (100 ml) and 1ml of low-level ISA are added into a 150 ml beaker.

4. Increments of the 10^{-2} M NaCl standard solution are added to the 150 ml beaker using steps outlined in Table 2.1. The potential (mV) is recorded when a stable reading is displayed. A calibration curve for low-level measurements of chloride is constructed similar to the Figure B.

5. A calibration curve for high-level measurements of chloride is constructed from potential reading resulting from serial dilution (see Table 2.2 and Figure C) of a 10^{-2} M NaCl standard .

6. A 20 μl sample is removed from Aq. II of transport experiment initially, every two hours for at least 10 hours. Each sample is diluted with 1.0 ml of a dilute ISA solution (1 ml of low-level ISA diluted to 100 ml with deionized H_2O). The potential reading of each sample is recorded. The total amount of Cl^- (in μmoles) transported into Aq. II is

calculated by multiplying the moles of Cl^- found in the diluted aliquot (as determined from the calibration curve) by 50.

7. The time course of chloride transport is plotted and the initial flux is determined from the linear region of concentration vs time curve.

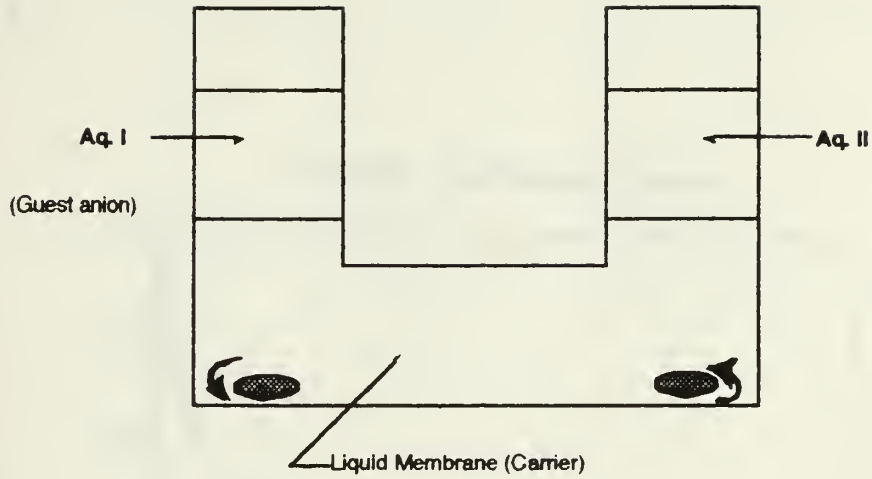
Table 2.1: Typical Calibration Data For Low-Level Measurements

Step	Added Std. Volume	Concentration Molarity (mole/l)	mV
1	0.1 ml	5.0×10^{-7} M	50.9
2	0.1 ml	1.0×10^{-6} M	45.2
3	0.2 ml	2.0×10^{-6} M	36.0
5	0.4 ml	5.0×10^{-6} M	28.9
6	2.0 ml	1.5×10^{-5} M	19.1
7	2.0 ml	2.4×10^{-5} M	-3.5
8	2.0 ml	3.3×10^{-5} M	-14.9
9	2.0 ml	4.1×10^{-5} M	-22.4
10	2.0 ml	4.9×10^{-5} M	-27.9
11	2.0 ml	5.7×10^{-5} M	-32.2
12	2.0 ml	6.5×10^{-5} M	-35.8
13	2.0 ml	7.2×10^{-5} M	-41.2
14	2.0 ml	8.2×10^{-5} M	-43.4
15	2.0 ml	8.7×10^{-5} M	-45.4

Table 2.2: Typical Calibration Data For High-Level Measurements

Step	Added H_2O Volume	Concentration Molarity (mole/l)	mV
1	(2 ml of 10^{-3} M standard only)	1.0×10^{-3} M	113.9
2	2.0 ml	5.0×10^{-4} M	-96.9
3	2.0 ml	3.33×10^{-4} M	-87.3
4	2.0 ml	2.5×10^{-4} M	-80.3
5	2.0 ml	2.0×10^{-4} M	-74.3
6	2.0 ml	1.66×10^{-4} M	-70.1
7	2.0 ml	1.43×10^{-4} M	-64.9

Figure A



A typical U-shaped glass tube cell for transport experiments.

Dimensions:

- diameter of each arm of the U-tube: 1.5 cm
- diameter of the bridge (between the two arms): 1.5 cm
- length of the bridge: 2.5 cm
- height of the U-tube: 9.0 cm -12 cm

Figure B

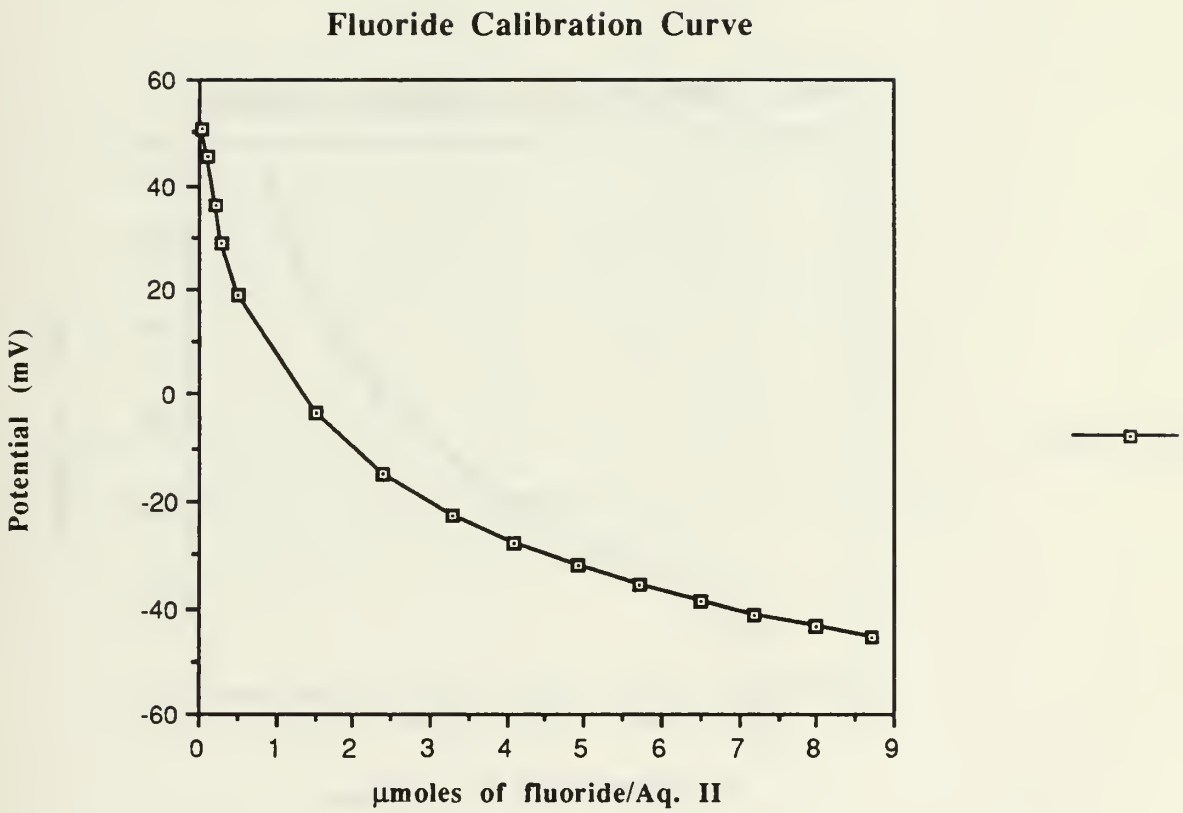
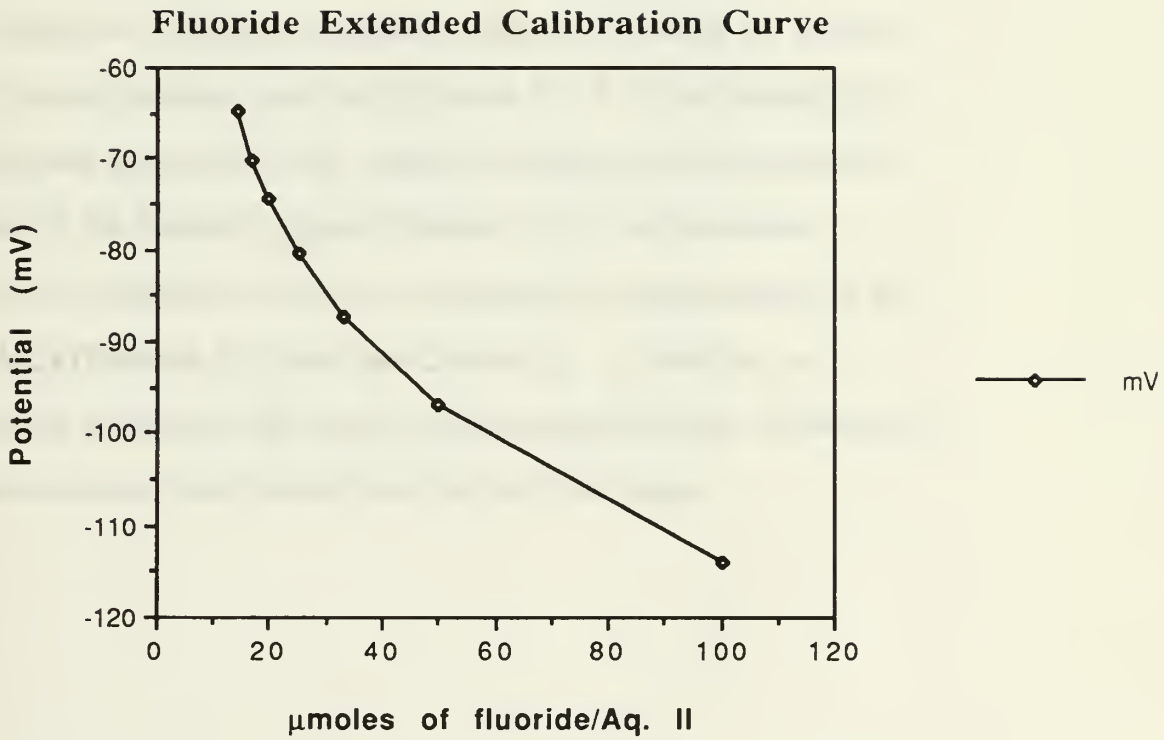

Fluoride Calibration Curve
Potential (mV)
60
40
20
0
-20
-40
-60
0
1
2
3
4
5
6
7
8
9
µmoles of fluoride/Aq. II

Figure C

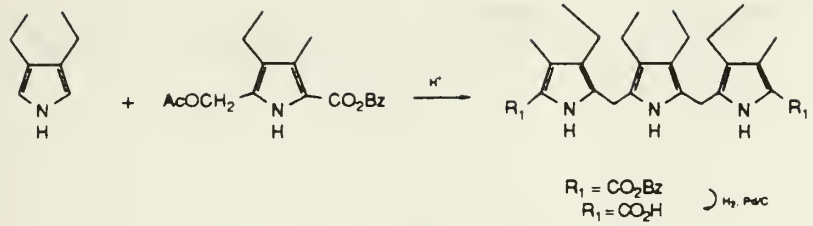

Fluoride Extended Calibration Curve
Potential (mV)
-60
-70
-80
-90
-100
-110
-120
0
20
40
60
80
100
120
µmoles of fluoride/Aq. II
mV

IV. Synthetic Schemes for Expanded Porphyrins Used as Carriers.

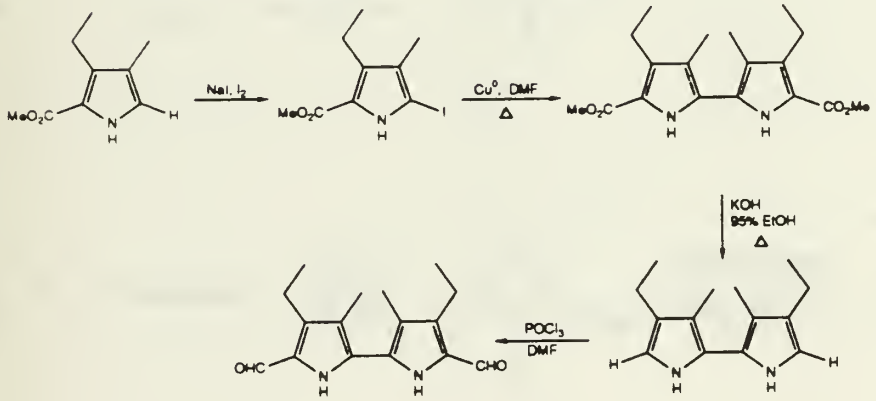
Sapphyrin (**27**) was prepared by the author using Dr. Micheal Cyr's improved synthetic method (Scheme 2.1).[5] Octaethylporphyrin (OEP,**28**) was prepared by Ms. Azadeh Mozaffari, a past laboratory technican of the Sessler's group (Scheme 2.2).[6] As previously mentioned, anthraphyrin (**29**) was prepared and characterized by Mr. Tarak Mody (Scheme 2.3, also see Chapter 4). In addition, he provided the texaphyrin (**30**) used in the transport studies (Scheme 4).[7] Synthetic schemes are provided on the next four pages.

Scheme 2.1

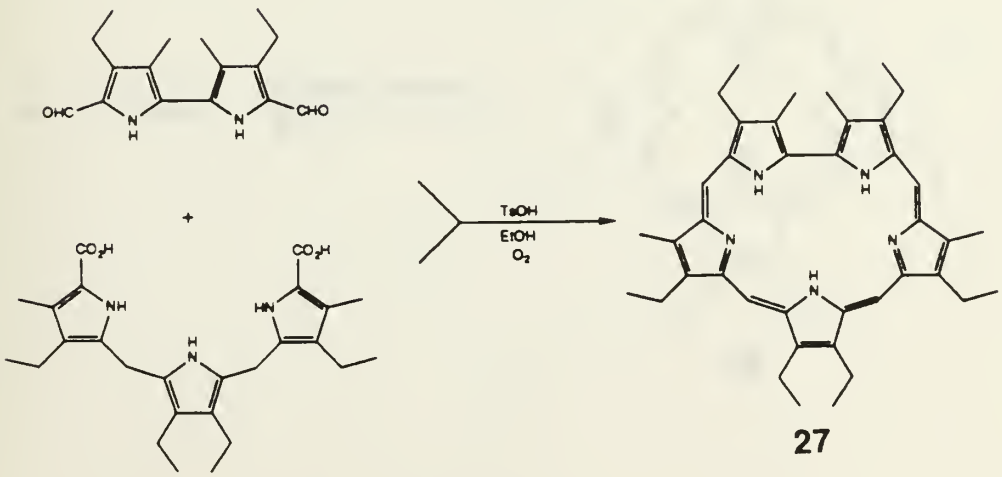
A



B.

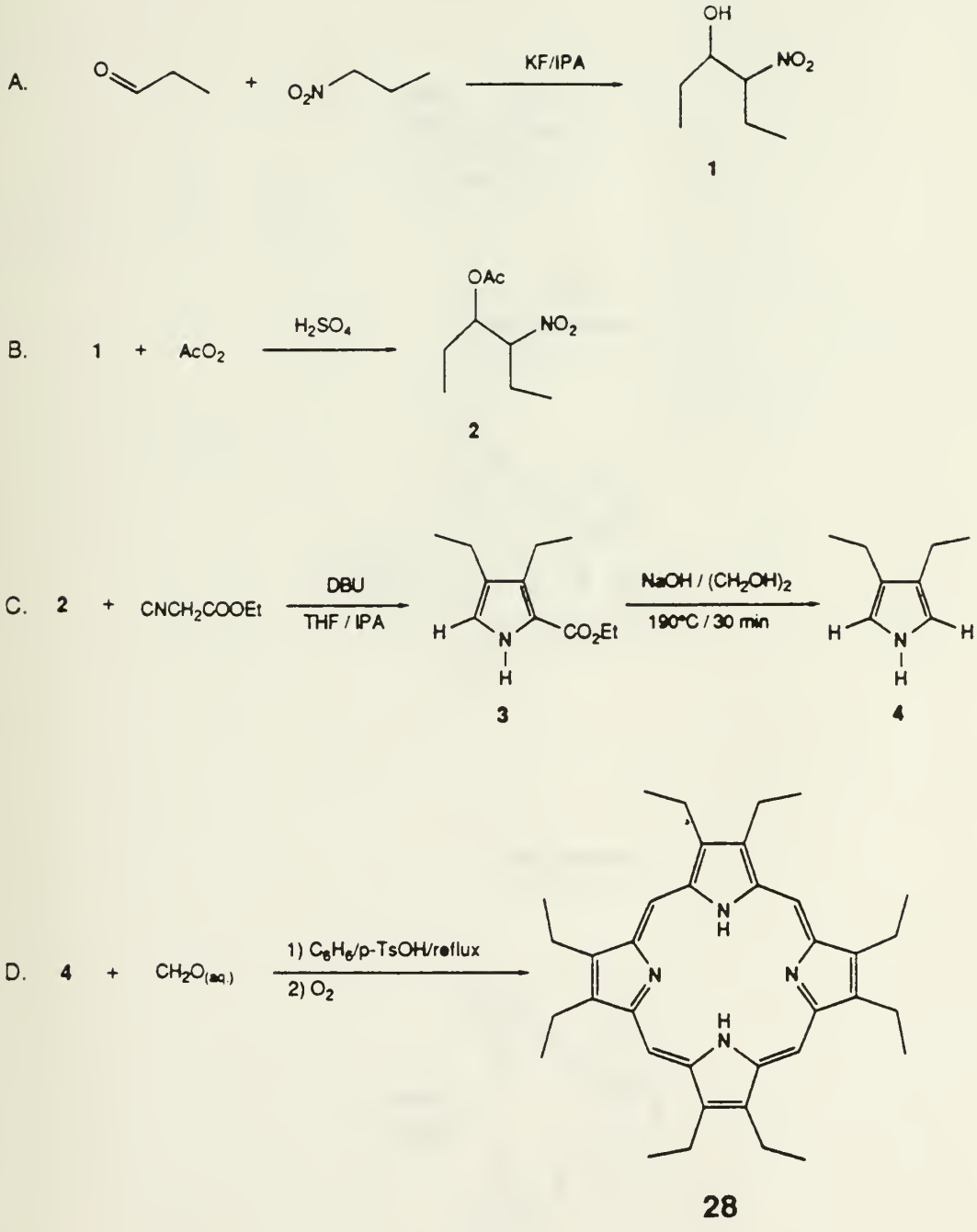


C.

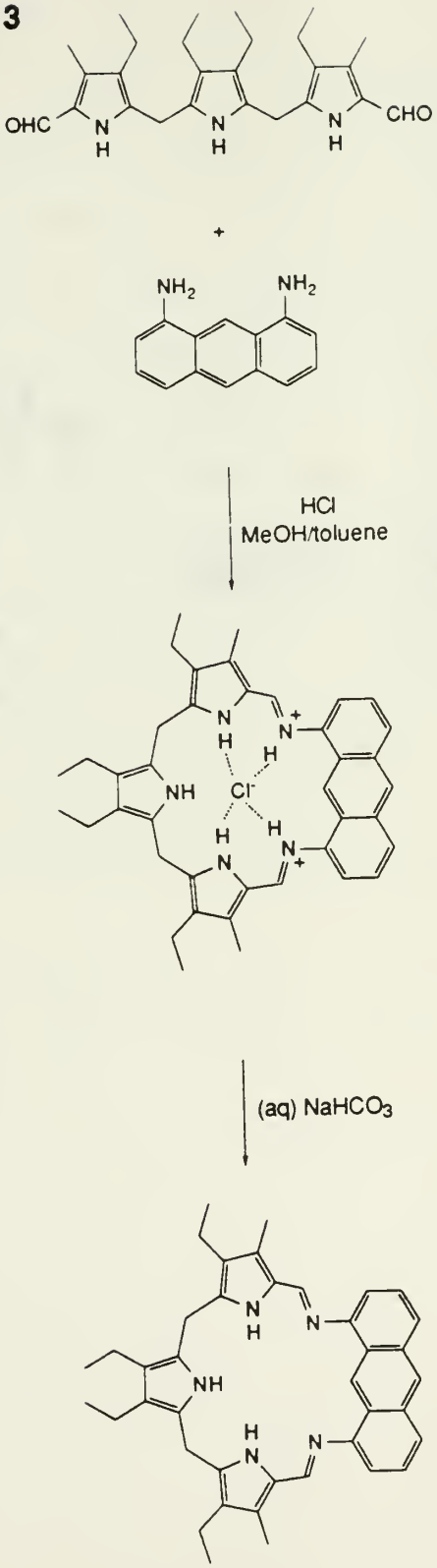


27

Scheme 2.2

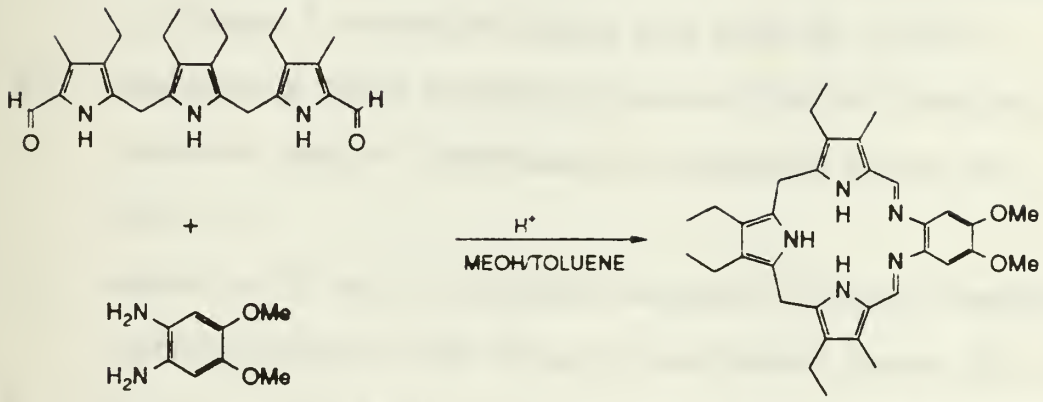

A.
KF/IPA
OH
NO2
1
B.
1 + AcO2
H2SO4
OAc
NO2
2
C. 2 + CNCH2COOEt
DBU
THF / IPA
CO2Et
NaOH / (CH2OH)2
190°C / 30 min
3
4
D. 4 + CH2O(aq.)
1) C6H6/p-TsOH/reflux
2) O2
28

Scheme 2.3



29

Scheme 2.4



30

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6. Sessler, J. L.; Mozaffari, A.; Johnson, M. R. *Org. Synth.* **1991,** *70,* 68-78.
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Chapter 3

Results: Sapphyrin and OEP as Carriers

Enhanced Transport of Fluoride Anion Effected Using Protonated Sapphyrin as a Carrier

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Sapphyrin, a large porphyrin-like macrocycle acts as an efficient carrier for the transport of fluoride anion in a model three-phase H_2O-CH_2Cl_2-H_2O bulk liquid membrane system.

The binding and through membrane transport of small anions plays an important role in many biological systems.[1] For instance, fluoride anion activation is important for a variety of enzymatic systems, including phosphatases, adenylate cyclase, and GTP-binding protein (G-protein).[2] In addition, mediated chloride anion transport is recognized as playing a crucial role in erythrocytes, where it serves to facilitate the excretion of CO_2 *via* a chloride/bicarbonate exchange process.[3] It has also recently been implicated in the function of the so-called cystic fibrosis transmembrane conductance regulator protein, CFTR.[4] However, in spite of their obvious importance, mechanistic studies of such anion receptor interactions in nature have so far been limited. They have been hampered, at least in part, by the unavailability of suitable model systems for anion binding and transport. Although numerous elegant anion-binding receptors have been reported in recent years,[5] the number of synthetic systems capable of achieving both anion binding and transport remains limited at present.[6] In this communication, therefore, we wish to report the through liquid membrane transport of fluoride anion effected

using the protonated form (H_4Sap^+) of sapphyrin (H_3Sap,**1**), a highly lipophilic porphyrin-like 22 π-electron macrocycle, as the carrier. To the best of our knowledge, such synthetic carrier-mediated fluoride transport is nearly without precedent in the anion recognition literature.[7]

⇒ insert structures **1** and **2** here

Recently, we reported the solid state complexation of F^- by the diprotonated form (H_5Sap^{2+}) of sapphyrin (**1**).[8] Specifically, from a single crystal X-ray analysis of the mixed F^-/PF_6^- salt, it was found that fluoride anion is encapsulated within the ca. 5.5 Å diameter core of the fully protonated macrocycle being held there by five NH-to-F hydrogen bonds. This finding, and the apparent lipophilicity of this and other anion-containing sapphyrin salts,[9] led us to consider that this "expanded porphyrin" could serve as a possible carrier for the through-membrane transport of F^-. As a test of this idea, we have explored F^- transport with H_5Sap^{2+} and H_4Sap^+ using a bulk liquid membrane system, Aq I-CH_2Cl_2-Aq II (Aq = aqueous), similar to that described earlier.[10,11]

The efficacy of F^- transport was first tested under conditions of an overall Aq I to Aq II proton gradient (Aq I: pH 3, Aq II: pH 12).[¶] Without an added carrier, slow uptake of F^- into Aq II by simple diffusion was observed (initial flux, $\phi = 4.0 \pm 0.4 \times 10^{-8}$ mol/h.) When sapphyrin (1.0 mM), however, was added to the central CH_2Cl_2 phase, F^- transport was enhanced strongly ($\phi = 86.0 \pm 8.6 \times 10^{-8}$ mol/h) (Figure 1). On the other hand, no or little acceleration was observed when octaethylporphyrin

(OEP, **2**), at the same concentration, was used as a "control" carrier (ϕ = 4.0 ± 0.4 x 10^{-8} mol/h). As expected, a decrease in the pH of Aq II was observed during sapphyrin mediated transport. This is consistent F^- transport occurring via the so-called symport mechanism,[12] in which fluoride anions and protons are co-complexed and co-transported by sapphyrin (Scheme 1A).

⇒ Insert Figure 1 and Scheme 1 here.

In order to get a clearer picture of F^- binding and transport, we have carried out similar transport experiments in the absence of a proton gradient ($pH_{Aq\ I} = pH_{Aq\ II}$). Under the conditions of these experiments, which were carried out using several different buffer systems and at several different pH regimes, both F^- and a buffer counter anion were expected to be transported in a so-called antiport process (Scheme 1B).[12] Although counter anion anti-transport was not specifically determined by the present experiments, the data from the sum total of these experiments (Table I) are certainly consistent with this hypothesis: Over the complete range of pH values investigated sapphyrin (**1**) was found to be an effective carrier for fluoride anion transport whilst its simple congener, (**2**), was not. Interestingly, the latter system in general proved no more effective than "pure" (carrier-free) CH_2Cl_2 in terms of enhancing the effective fluoride anion transport rate (Table 1). Presumably, this reflects the fact that protonated porphyrins (nitrogen-to-nitrogen core: size ca. 4.0 Å[13]), protonated or otherwise, are too small for effective in-plane fluoride anion

complexation, while, as noted above, diprotonated sapphyrin can and does bind F^- in the solid state.[8]

⇒ Insert Table 1 here.

As might be expected, some dependence on the choice of buffer and pH is observed for the transport experiments summarized in Table 1. First, fluoride anion transport is enhanced, both for sapphyrin and the controls, when a more lipophilic buffer system is used to define the aqueous phase pH values. Second, as is consistent with the observed pKa values for sapphyrin,[¶] fluoride anion transport with this carrier was found to be enhanced at pH 3 (where H_5Sap^{2+} is the dominant species) and nearly independent of aqueous phase pH in the 5-9 pH regime (wherein H_4Sap^+ dominates among possible sapphyrin species). Taken together, these data provide further support for the proposed anti-port mechanism (Scheme 1B) and confirm the efficacy of this particular "expanded porphyrin" as a fluoride anion transport carrier.

Addition of chloride anion to the present transport system, under either symport or antiport conditions, caused a slight inhibition in the observed fluoride anion transport rates. Presumably, this reflects the effect of competitive chloride anion binding by sapphyrin and/or its protonated derivatives. At present, therefore, we are exploring the ability of sapphyrin and its protonated derivatives to function as a transport carrier agent for this and other small anions. In preliminary work[⊥] we have found that chloride anion transport may be effected using monoprotonated sapphyrin, H_4Sap^+, as the carrier species[⊥] whereas the corresponding

diprotonated form, H_5Sap^{2+}, (only) acts as an efficient carrier for guanosine-5'-monophosphate dianion.[11] Full details of these and other transport-related studies will be reported in due course.

This work was supported by the Texas Advanced Research Program (grant no. 3658-016). J.L.S. also thanks the National Science Foundation (PYI 1986), the Camille and Henry Dreyfus Foundation (Teacher-Scholar 1988-1993), and the Sloan Foundation (Fellowship 1989-1991). D.A.F. thanks the United States Navy for the educational opportunity.

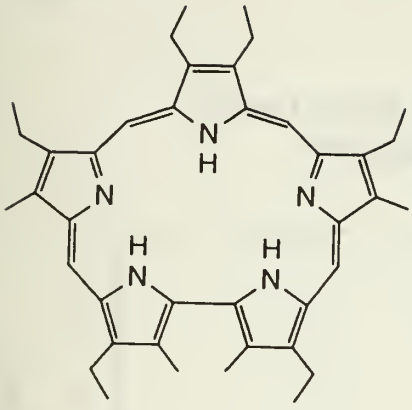
Footnotes

¶. The first and second pKa values of diprotonated sapphyrin have been determined as being ca. 3.5 (Sap^{2+}/Sap^{+}) and 9.5 (Sap^{+}/Sap), respectively; see ref. 11

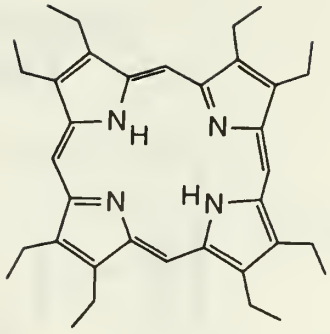
#. Initial flux values, ϕ, were calculated from the amount (μmoles) of Cl^- and F^- transported per hour during the initial linear kinetic regime; see ref. 10.

⊥. For Cl^- transport at pH 7.0, an initial flux value, ϕ, of $48.0 \pm 0.5 \times 10^{-8}$ mol/h was obtained.

Structures

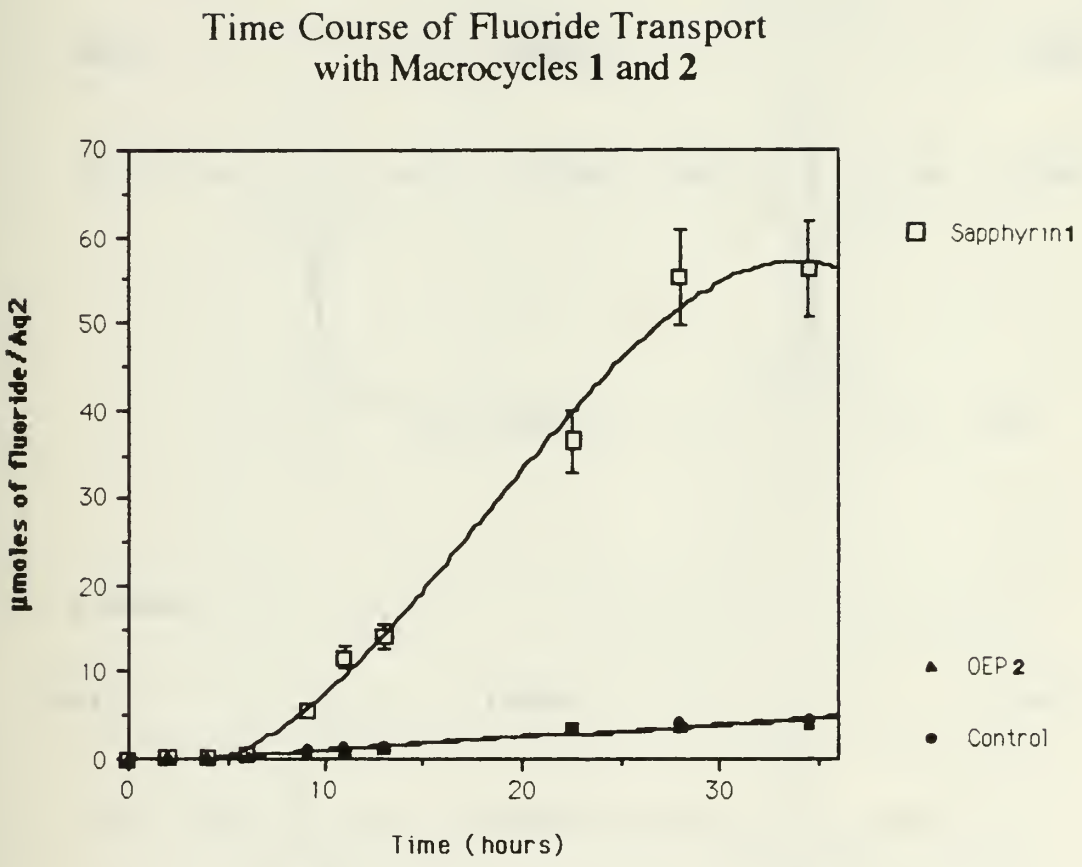


1



2

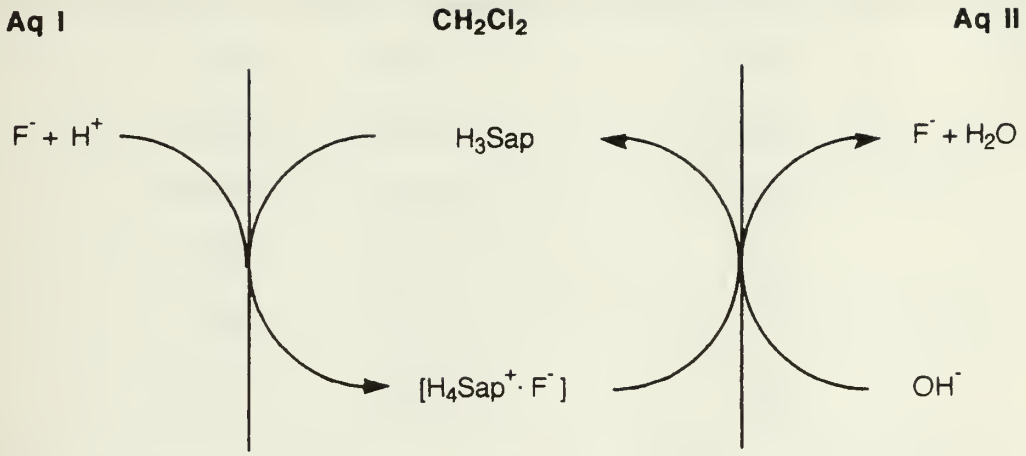
Figure 1



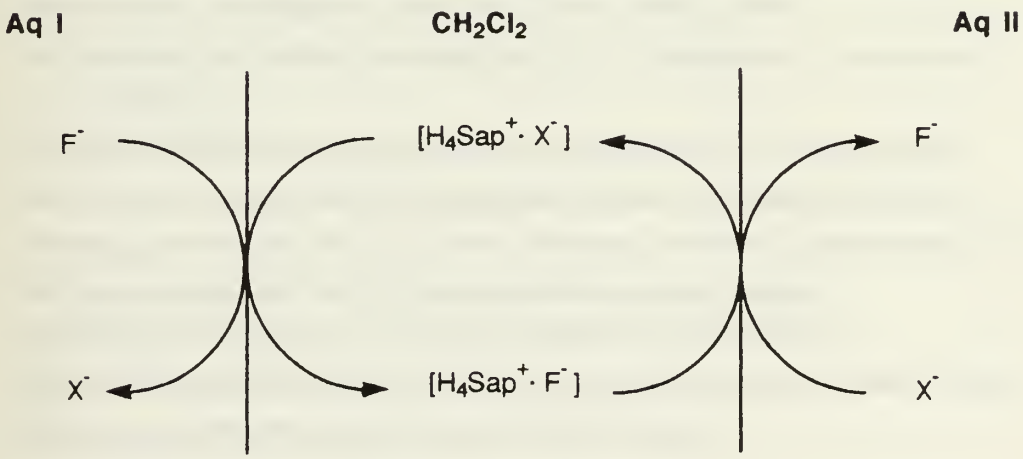
Caption to Figure. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.5 M HF, adjusted to pH 3.2 with NaOH. Membrane (10 mL); carrier: 1.0 mM in CH_2Cl_2. Aq II (1mL); NaOH (pH 12). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier. Error is within ±10%.

Scheme 1

A: Symport



B: Antiport



H_4Sap^+ = monoprotonated Sapphyrin (H_3Sap,**1**); X^- = CH_3COO^-,CF_3COO^-,$H_2NCH_2COO^-$, etc .

Table 1. Initial fluoride transport flux Φ[a)]

Exp#	pH(Aq I and Aq II)[b)]	Sapphyrin (**1**) Φ (10^{-8}mol/h)	OEP (**2**) Φ (10^{-8}mol/h)	Control [c)] Φ (10^{-8}mol/h)
1	3.0 [d)]	11.8	4.7	4.7
2	3.0 [e)]	17.6	0.8	0.1
3	5.0 [f)]	4.9	0.6	0.3
4	7.0 [g)]	9.5	0.3	0.1
5	7.0 [h)]	2.5	1.2	1.2
6	9.0 [i)]	10.7	0.6	0.3

a) Transport experiments were performed in a manner similar to those reported in ref. 10. [NaF] = 0.25 M; [Carrier] = 1 mM. Initial transport flux (Φ) were calculated from the linear region of concentration vs time curve. Error is within ± 10%.

b) Aq I containing NaF buffered at the specified pH; Aq II contained only buffer solution at the specified pH.

c) Transport experiments conducted under specified conditions in the absence of carrier.

d) Buffered at specified pH with trifluoroacetic acid/ sodium trifluoroacetate solution.

e) Adjusted to specified pH with 0.1 M acetic acid/sodium acetate and a small amount of dilute HF.

f) Buffered at specified pH with 0.2 M acetic acid/sodium acetate solution.

g) Adjusted to specified pH with 1.5 M acetic acid/sodium acetate solution.

h) Buffered at specified pH with 0.2 M tris(hyroxymethyl)aminomethane-maleate solution.

i) Buffered at specified pH with 0.2 M glycine-NaOH solution.

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Supplementary Material

For

" Enhanced Transport of Fluoride Anion Effected Using Protonated Sapphyrin as Carrier."

Jonathan L. Sessler*, Debra A. Ford, Michael J. Cyr,
and Hiroyuki Furuta

Department of Chemistry and Biochemistry,
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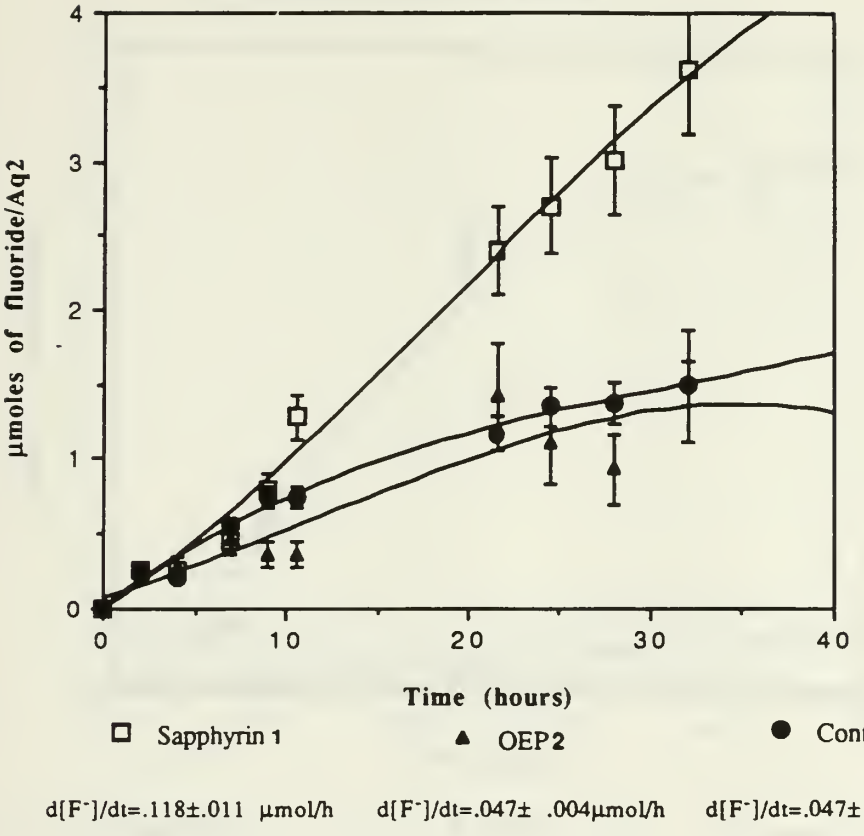
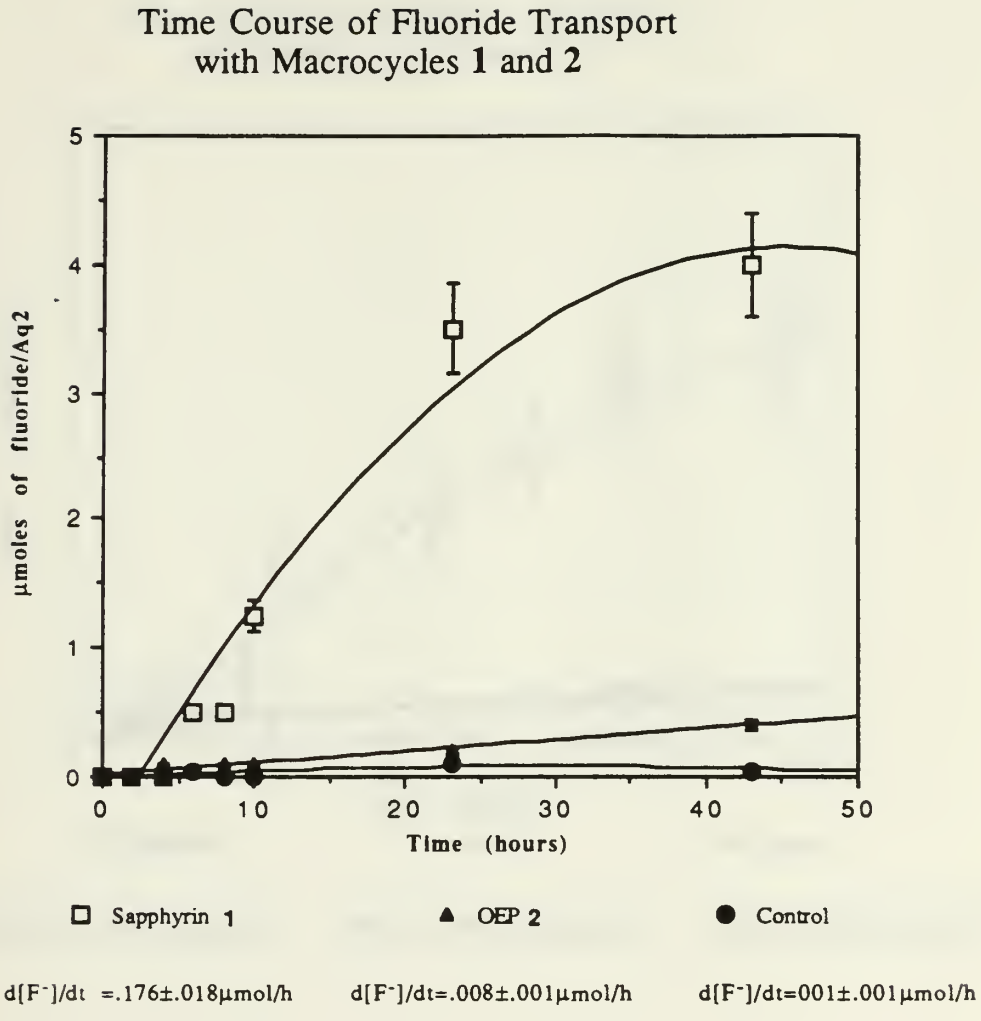
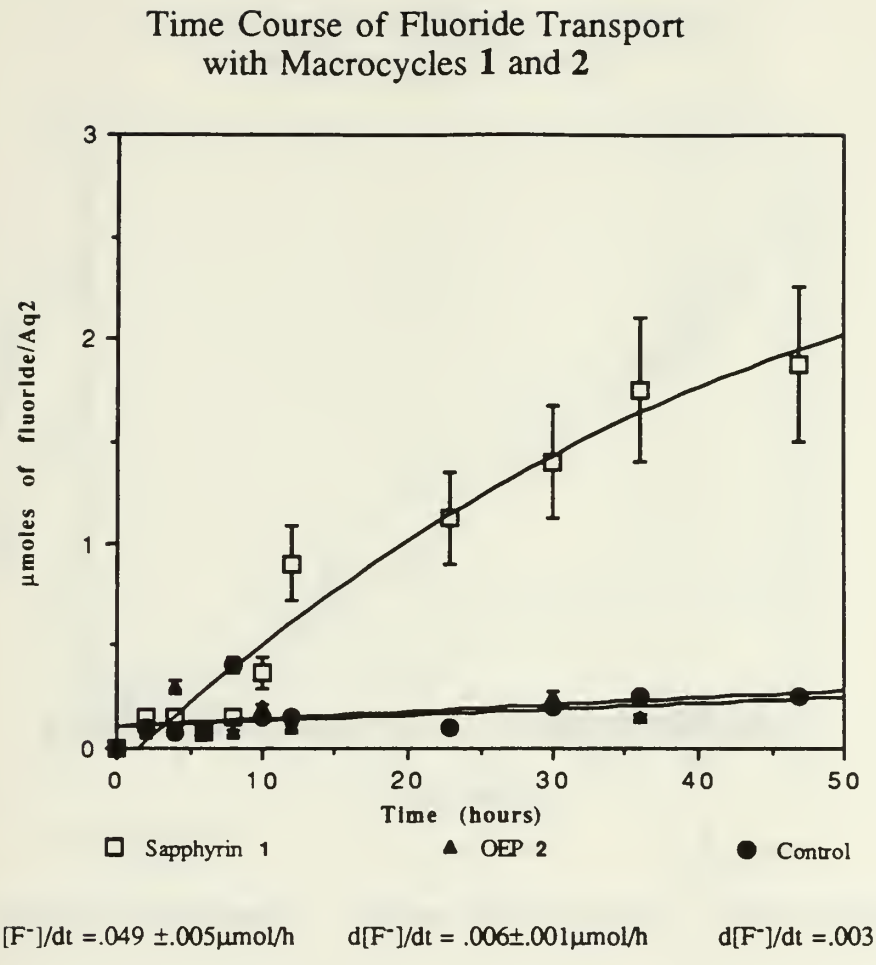
Time Course of Fluoride Transport
with Macrocycles **1** and **2**



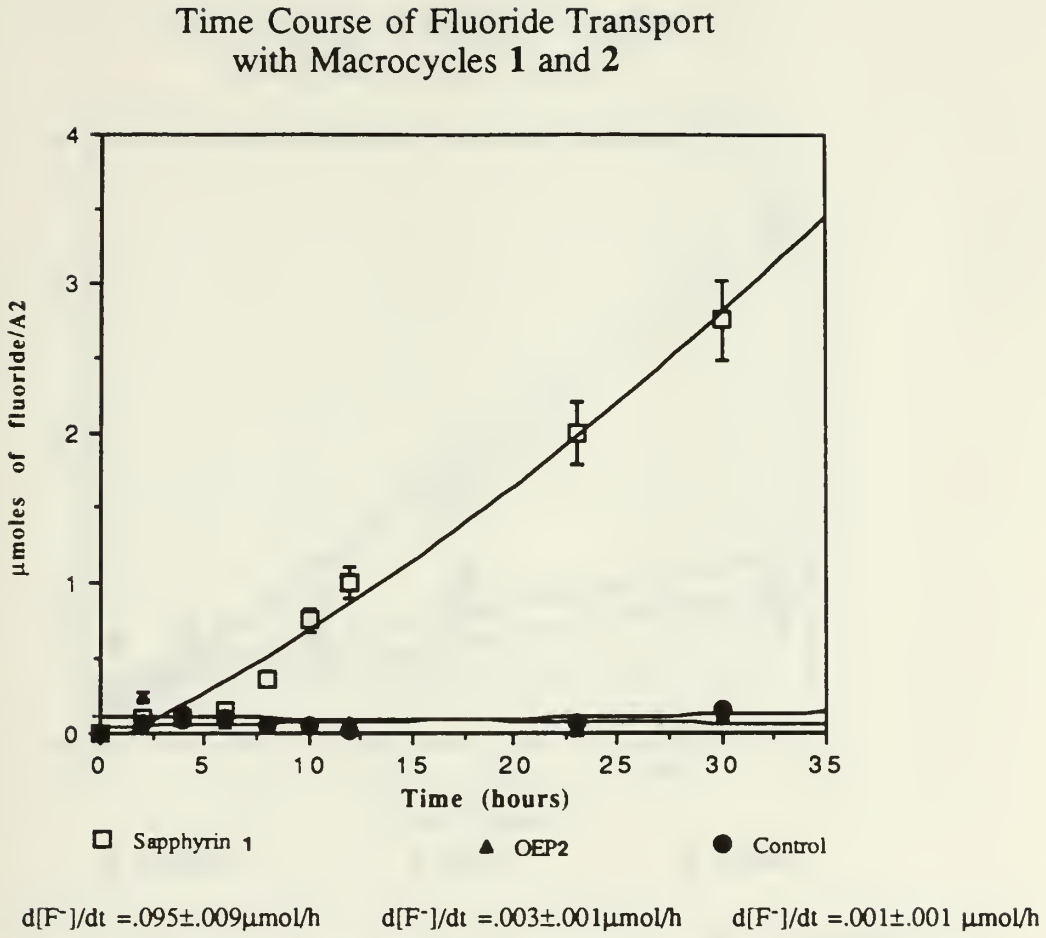
Supplementary Figure 1. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.25M NaF, buffered to pH 3.0 using Trifloroacetic acid and NaOH. Membrane; carrier: (10 mL) 1.0 mM in CH_2Cl_2. Aq II(1mL); Trifloroacetic acid buffer (pH 3.0). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.



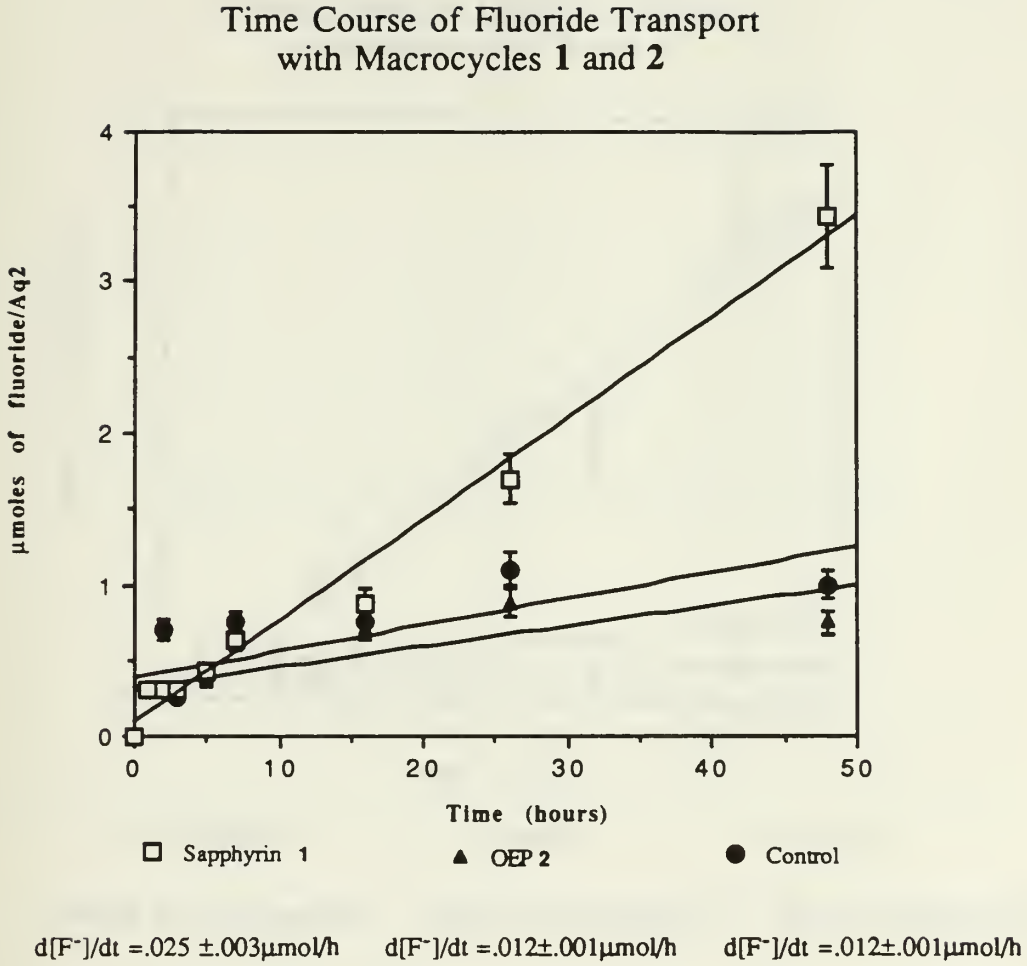
Supplementary Figure 2. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.25M NaF, buffered to pH 3.0 with acetic acid and sodium acetate. Membrane(10ml); carrier: 1.0 mM in CH_2Cl_2. Aq II(1mL); Acetic acid buffer (pH 3.0). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.



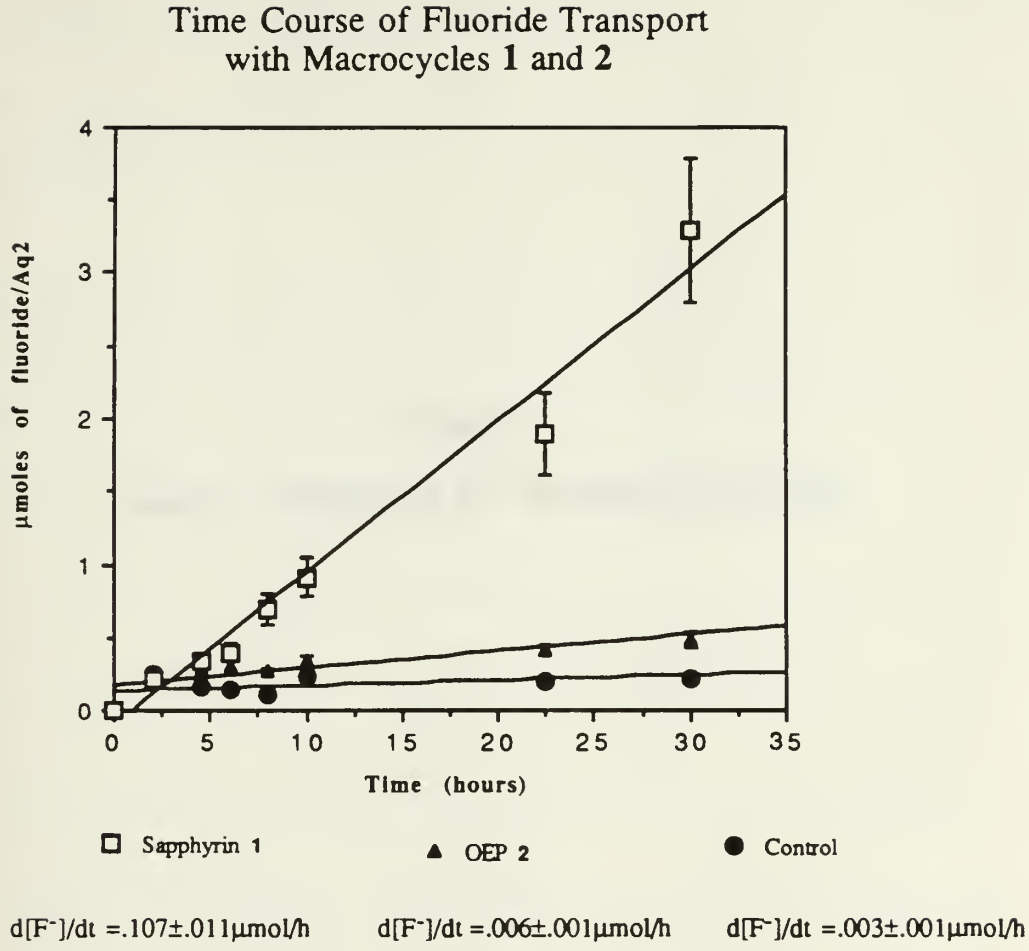
Supplementary Figure 3. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.25M NaF, buffered to pH 5.0 (with Acetic acid) Membrane(10ml); carrier: 1.0 mM in CH_2Cl_2. Aq II(1mL); Acetic acid buffer (pH 5.0). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.



Supplementary Figure 4. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.25M NaF, buffered to pH 7.0 with acetic acid and sodium acetate. Membrane (10ml); carrier: 1.0 mM in CH_2Cl_2. Aq II(1mL); Acetic acid buffer (pH 7.0). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.



Supplementary Figure 5. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.25M NaF, buffered to pH 7.0 (with tris(hydroxymethyl) aminomethane-maleate) Membrane; carrier: 1.0 mM, 10 mL CH_2Cl_2. Aq II(1mL); Tris-maleate buffer (pH 7.0). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.



Supplementary Figure 6. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.25M NaF, buffered to pH 9.0 (with glycine-NaOH) Membrane(10ml); carrier: 1.0 mM in CH_2Cl_2. Aq II(1mL); Glycine-NaOH buffer (pH 9.0). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.

Chapter 4

Results: Anthraphyrin and Texaphyrin as Carriers

A Non-aromatic Anthracene Derived "Expanded Porphyrin": An Unexpected Anion Binding Agent.

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Department of Chemistry and Biochemistry, University of Texas, Austin, Texas 78712

Abstract. The synthesis, characterization, and X-ray diffraction structure of the mixed $HCl{\cdot}HBF_4$ salt (**2**$\cdot BF_4$) of a novel non-aromatic anthracene derived "expanded porphyrin," 4,5,9,31-tetraethyl-10,30-dimethyl-13,27,32,33,34-pentaazaheptacyclo[27.2.1.1^{3,6}.1^{8,11}. 1^{18,22}.0^{14,19}. 0^{21,26}]pentatriaconta-3,5,8,10,12,14,16,18,20,22(35),23,25,27,29,31-pentadecaene (**1**) which contains chloride anion centrally encapsulated in the solid state are reported. The synthesis involves, as the critical step, an acid catalyzed 1:1 Schiff-base condensation between 1,8-diaminoanthracene **4** and 2,5-bis((3-ethyl-5-formyl-4-methylpyrrol-2-yl) methyl)-3,4-diethylpyrrole **3**. The tetrafluoroborate salt of **2** (**2**$\cdot BF_4$) crystallizes in the triclinic space group $P\bar{1}$ (No. 2) in a cell of dimensions: a = 10.695(3), b = 12.048(3), c = 14.774(4)Å, α = 81.35(2), β = 74.36(2), γ = 88.75(2)°, V = 1811.8(9)Å^3, with Z = 2, ρ_{calc} = 1.32 g cm^{-3} (198 K). Of the 6418 unique reflections, 4269 reflections with $F_o^2 > 3\sigma(F_o^2)$ were used to refine the structure to a final R = 0.0465, wR = 0.0560, and a goodness of fit = 1.840 for 640 parameters. The macrocycle is composed of two planar portions that are nearly orthogonal (dihedral angle 79.3(3)°). The bound Cl^- ion sits slightly above the larger portion of the macrocycle (0.795(1)Å above the plane through the donor N atoms) and is H-bonded to four NH groups while a BF_4^- ion is H-bonded to the remaining pyrrole NH group. Compound **1** at a concentration of 1.0 mM was

found to be an effective carrier for the through-CH_2Cl_2 transport of fluoride anion in a three-phase model membrane systems consisting of [0.5 M HF, adjusted to pH 3.2 with NaOH]-CH_2Cl_2-[NaOH, pH 12] ($d[F^-]_{trans.}/dt = 6.41 \pm 0.21$ $\mu mol/cm^2 \cdot h$), but relatively less so for chloride anion transport under similar experimental conditions ($d[Cl^-]_{trans.}/dt = 1.98 \pm 0.21$ $\mu mol/cm^2 \cdot h$). In addition, fluoride anion transport by **1** was found to be strongly inhibited by chloride anion. These results are rationalized in terms of a strong, non-labile chloride complex being formed between Cl^- and the protonated form of **1**.

A Non-aromatic Anthracene Derived "Expanded Porphyrin": An Unexpected Anion Binding Agent.

Jonathan L. Sessler,* Tarak D. Mody, Debra A. Ford, and Vincent Lynch

Department of Chemistry and Biochemistry, University of Texas, Austin, Texas 78712

Porphyrins are among the most versatile ligands, forming complexes with almost every metal cation in the periodic table.[1] However, little record of these species as anion binding agents[2] has appeared in the literature.[3-5] One reason, perhaps, is that protonated porphyrins, with a core diameter of approximately 4 Å, are too small to bind anions within the macrocyclic cavity.[2] Quite recently, we have found that certain aromatic "expanded porphyrins" including, sapphyrin,[6] and rubyrin[7] are capable of serving as anion binding receptors in the solid state. Here, we wish to report the synthesis and crystallographic characterization of a novel non-aromatic anthracene derived Schiff base "expanded porphyrin," **1**, which when diprotonated effectively binds chloride anion in the solid state.[8-10] In addition, we present the results of liquid-membrane transport experiments consistent with chloride and fluoride binding in solution.

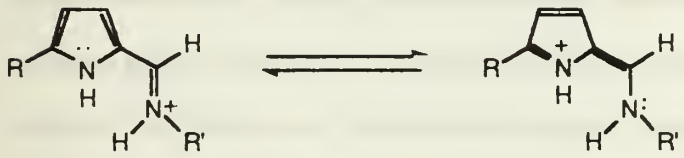
The synthesis of macrocycle **2**·Cl and its neutral parent, **1**, is shown in Scheme 1. It involves, as the critical step, the acid catalyzed 1:1 Schiff-base condensation between 1,8-diaminoanthracene **4**[9] and the diformyl tripyrrane **3**.[11] X-ray quality crystals of the diprotonated macrocycle, as its mixed chloride tetrafluoroborate salt [**2**·BF_4] were obtained by slow vapor diffusion of diethyl

ether into a dichloromethane/methanol (2:1 v/v) solution containing **2**·Cl and a small excess of ethereal tetrafluoroboric acid.[10]

From the X-ray diffraction analysis, the core of the macrocycle is found to contain a near mirror plane with the two pyrrole rings A and C of the tripyrrane and the anthracene moiety lying in essentially the same plane (Figure 1). On the other hand, the central pyrrole ring B is tilted away, almost perpendicular, to the mirror plane. The dihedral angle between this central pyrrole and the remainder of the macrocycle is 79.3°. The chloride anion is bound in a pseudo-square planar geometry 0.795 Å above the planar portion of the macrocycle with the four inner hydrogen atoms (H(13), H(27), H(32), H(34)) pointing towards it. The H-Cl hydrogen bonding distances range from 2.21(4) Å to 2.41(4) Å. The N-Cl bond distances range between 3.11 Å to 3.25 Å , and are consistent with such distances expected for strong hydrogen bonding.[2d] There is also a hydrogen bonding interaction between F(4) of the BF_4^- and H(33)N(33) of the central pyrrole. In this case the H-F bond distance is 2.02(3) Å.

The structure of the chloride-containing salt **2**·BF_4 differs from that of the HSCN salt (**6**) of our earlier-reported non-aromatic texaphyrin-type system **7**.[11] For instance, the latter is clearly mono-protonated at one of the imine nitrogens whereas **2**·BF_4 is clearly quite stable as a diprotonated salt in the solid state. This may simply reflect effective differences in basicity resulting from the two different imine(N)-imine(N) distances (5.024(1) Å and 2.60(1) Å) present in **2**·BF_4 and **6**, respectively. In particular, we suggest that two protons can be accommodated in the plane of macrocycle **1**, whereas in **7**, geometric and/or electrostatic repulsions

would preclude such a double accommodation.[12] Certainly, in **2**·BF_4, the short bond distances between C(11)-C(12) and C(28)-C(29) (1.373 Å and 1.386 Å, respectively) are consistent with a model wherein the positive charges on the imminium centers (N(13) and N(27)) are delocalized into the adjacent pyrroles (rings A and B) as per eq 1.



(1)

In contrast to other comparable expanded porphyrin anion adducts (e.g. **6**), the core chloride complex of **2**·BF_4 (cation **2**) was detected in both the low resolution and high resolution fast atom bombardment (FAB) mass spectra of **2**·BF_4.[9] These data lead us to suggest that the chloride anion is bound tightly in **2**·BF_4, at least in gas phase.

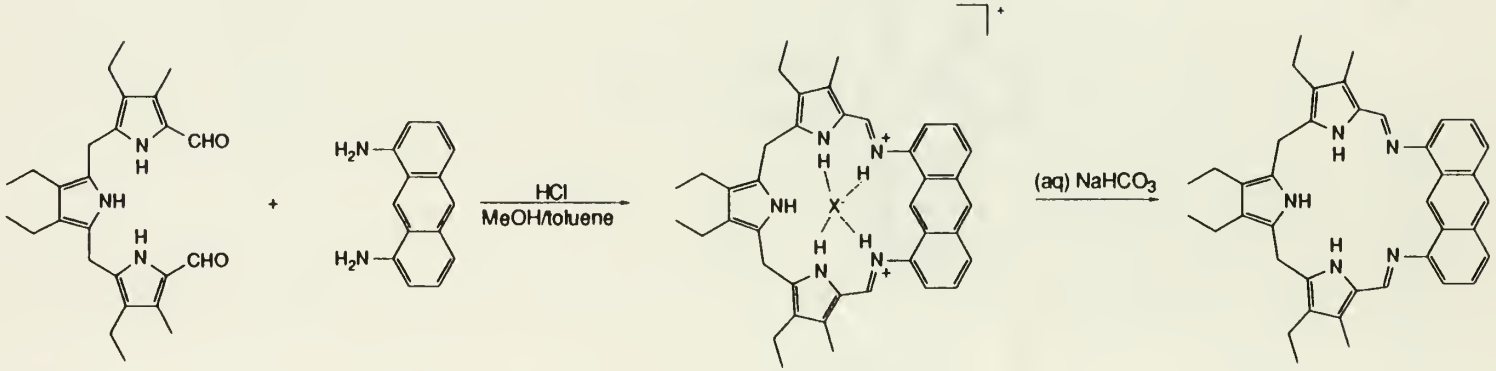
Further insight into the anion binding behavior of macrocycle **1** and its protonated derivatives[13] was obtained from preliminary solution phase transport experiments using a three-phase [Aq I]-[CH_2Cl_2]-[Aq II] model membrane system (Aq = Aqueous). In a first set of experiments, with Aq I = 0.5 M HF, adjusted to pH 3.2 with NaOH,[14] and Aq II = NaOH, (pH 12), compound **1** was found to accelerate the through-CH_2Cl_2 transport of fluoride anion with a transport rate ($d[F^-]_{trans}/dt$) of 6.41 ± 0.21 μmol/cm^2·h)[15] under conditions

where the hydrolytically stable "control" system **8**[17,18] proved much less effective as a carrier ($d[F^-]_{trans}/dt = 2.04 \pm 0.10$ μmol/cm^2·h) and simple passive diffusion (in the absence of any added carrier) was negligible ($d[F^-]_{trans}/dt \leq 0.01$ μmol/cm^2·h). This fluoride anion transport was strongly inhibited by chloride anion. For instance, with Aq I = 0.5 M HF + 0.5 M NaCl (pH 3.2); Aq II = NaOH, (pH 12), the transport rate was $d[F^-]_{trans}/dt = 1.30 \pm 0.10$ μmol/cm^2·h. This could reflect the fact that fluoride anion transport is limited by the formation and/or break-up of a strong, rather non-labile chloride complex under these solution phase conditions. Consistent with this supposition is the finding that **1** is relatively ineffective as a chloride anion carrier, being only nominally better than **8** ($d[Cl^-]_{trans}/dt = 1.98 \pm 0.21$ μmol/cm^2·h and 1.44 ± 0.21 μmol/cm^2·h for **1** and **8**, respectively; Aq 1 = 0.1 M HCl + 0.4 M NaCl (pH 1.2); Aq II = NaOH, (pH 12). Currently, we are exploring further the solution phase anion binding behavior of this and other related expanded porphyrin type macrocycles.[19]

Acknowledgement. This work was supported by an NIH grant (AI 28845), an NSF Presidential Young Investigator Award (1986), an Alfred P. Sloan Foundation Research Fellowship (1989-1991), and a Camille and Henry Dreyfus Foundation Teacher-Scholar Award (1988-1992) to J.L.S. J.L.S. and T.D.M. are grateful to Dr. Hiroyuki Furuta for assisting with the transport experiments, and to Ken Lancaster for synthetic assistance. Also, we would like to thank Takashi Morishima and Mitsubishi Kasei Co. for the sample of 1,8-diaminoanthraquinone.

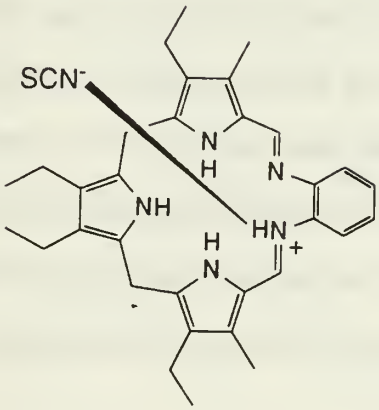
Supplementary Material Available. Synthetic experimental details for compounds **1**, **2**·Cl, and **4**, X-ray experimental data for **2**·BF_4 , and tables of atomic thermal factors, atomic positional parameters, bond distances and angles for **2**·BF_4 (34 pages); listing of observed and calculated structure factor amplitudes for **2**·BF_4 (23 pages). Ordering information is given on any current masthead page.

Scheme 1

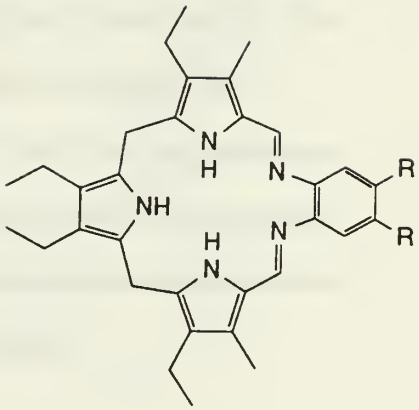


3 4 2. $X^- = Cl^-$ 5. $X^- = F^-$ 1

Structures



6

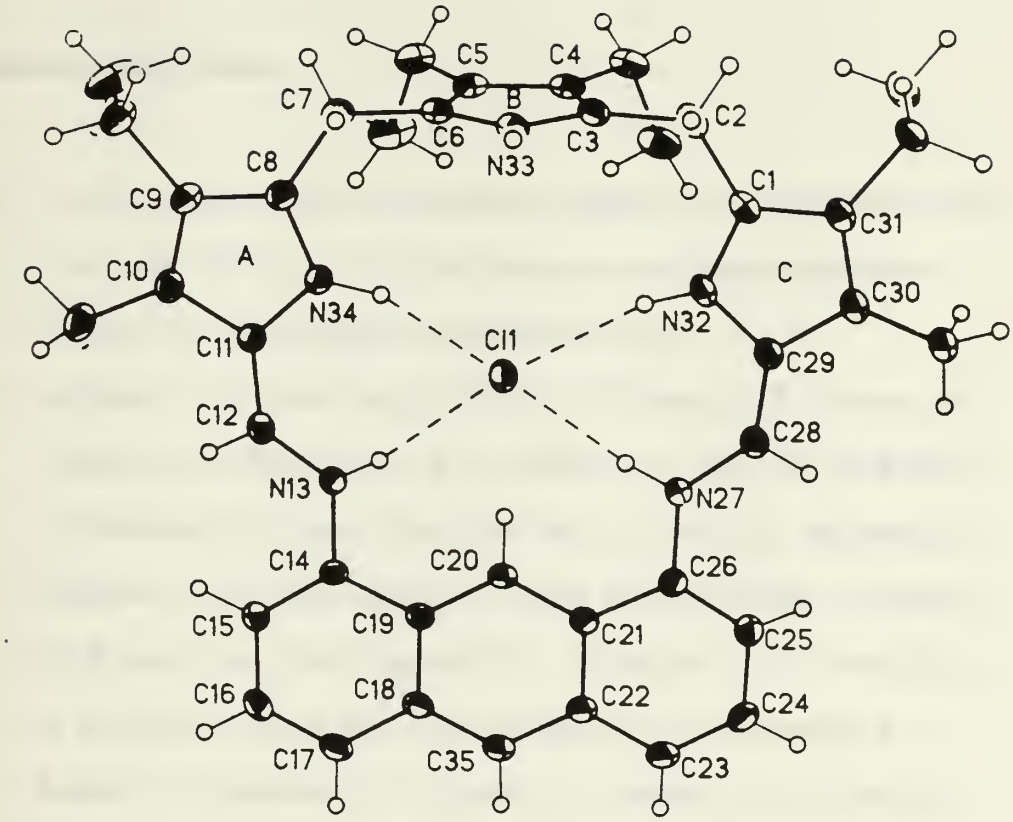


7. R = H
8. R = OCH_3

Caption to Figure

Figure 1. Molecular structure of **2**·BF_4 showing partial atom labelling scheme and the H-bonding interactions of the Cl^- counterion with the macrocycle (dashed lines). Not shown is a BF_4^- counter anion H-bound 2.02(3) Å from, and nearly directly above, N(33) of pyrrole ring B. The thermal ellipsoids are scaled to the 30% probability level while the hydrogen atoms are scaled to an arbitrary size. Top: View perpendicular to the plane through the nitrogen atoms. Bottom: Side view showing the nearly perpendicular orientation of the two planar subunits macrocycle and the partial encapsulation of the chloride counter anion.

Figure 1


C5
C4
C7
B
C2
C6
C3
N33
C8
C1
C9
C31
A
C
C10
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N32
Cl1
C11
C29
C12
C28
N13
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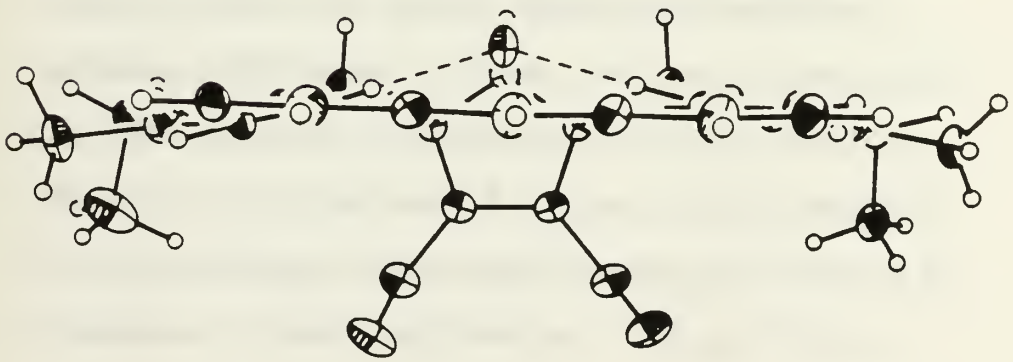

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(8) The systematic name for macrocycle **1** is: 4,5,9,31-tetraethyl-10,30-dimethyl-13,27,32,33,34-pentaazaheptacyclo[27.2.1.1^{3,6}.1^{8,11}.1^{18,22}.0^{14,19}.0^{21,26}]pentatriaconta-3,5,8,10,12,14,16,18,20,22(35),23,25,27,29,31-pentadecaene. We suggest the trivial name, anthraphyrin, for this compound.

(9) Satisfactory spectroscopic and mass spectrometric data were obtained for all new compounds (c.f. Supplementary Material).

(10) Crystal data: $(C_{40}H_{45}N_5)^{2+}(Cl^-)(BF_4^-)$; triclinic, $P\bar{1}$ (No. 2), Z = 2 in a cell of dimensions: a = 10.695(3), b = 12.048(3), c = 14.774(4)Å, α = 81.35(2), β = 74.36(2), γ = 88.75(2)°, V = 1811.8(9)Å^3, ρ_{calc} = 1.32 g cm^{-3} (198 K), F(000) = 756. Data collected at 198 K on a Nicolet R3 diffractometer, graphite monochromatized Mo Kα radiation (λ = 0.7107Å) using the ω-scan technique out to 50° in 2θ; 6418 unique reflections, 4269 with $F_o^2 > 3\sigma(F_o^2)$. The structure was solved by direct methods and refined by full-matrix least-squares (SHELXTL-Plus, Siemens Analytical X-ray Instruments, Inc., Madison, WI, USA) with anisotropic thermal parameters for the non-hydrogen atoms. Hydrogen atoms were obtained from a ΔF map and refined isotropically. The final R = 0.0465, wR = 0.0560, goodness of fit = 1.840 for 640 parameters.

The minimum and maximum peaks in the final ΔF map were -0.26, 0.31 $e^- Å^{-3}$, respectively.

(11) Sessler, J. L.; Johnson, M. J.; Lynch, V. *J. Org. Chem.* **1987**, *52*, 4394-4397.

(12) The structure of **2**·BF_4 also differs from that of the dihydrochloride salt of tetrapyridyl porphyrin. This latter system binds one chloride anion each above and below the macrocyclic plane. (See ref. 2d)

(13) The pKa values of the diprotonated anthraphyrin, pKa_1 and pKa_2 were found to be 4.0 and 8.5, respectively.

(14) The [F^-] was calculated to be approximately 0.25 M under these conditions ($Ka_{HF} = 6.46 \times 10^{-4}$ M); *The Merck Index*, 11 ed.; Merck & Co.; Rahway, N. J., 1989.

(15) In all cases the carrier concentration in the membrane was 1.0 mM (10 ml CH_2Cl_2). The release of anions (F^- and/or Cl^-) into the receiving phase, Aq II (1 mL) was monitored using fluoride and/or chloride electrodes (Orion). Transport rates ($d[X^-]_{trans.}/dt$) were calculated from the amount (μmoles) of Cl^- and F^- transported per hour during the initial linear kinetic regime (see ref. 16).

(16) Furuta, H.; Furuta, K.; Sessler, J. L. *J. Am. Chem. Soc.* **1991**, *113*, 4706-4707.

(17) The dimethoxy derivative **8**[18] was used in place of **7** as it proved more (and sufficiently) hydrolytically stable.

(18) Sessler, J. L.; Mody, T. D.; Ramasamy, R.; Sherry, A. D. *New J. Chem.*, in press.

(19) Furuta, H.; Cyr, M. J.; Sessler, J. L. *J. Am. Chem. Soc.*, in revision.

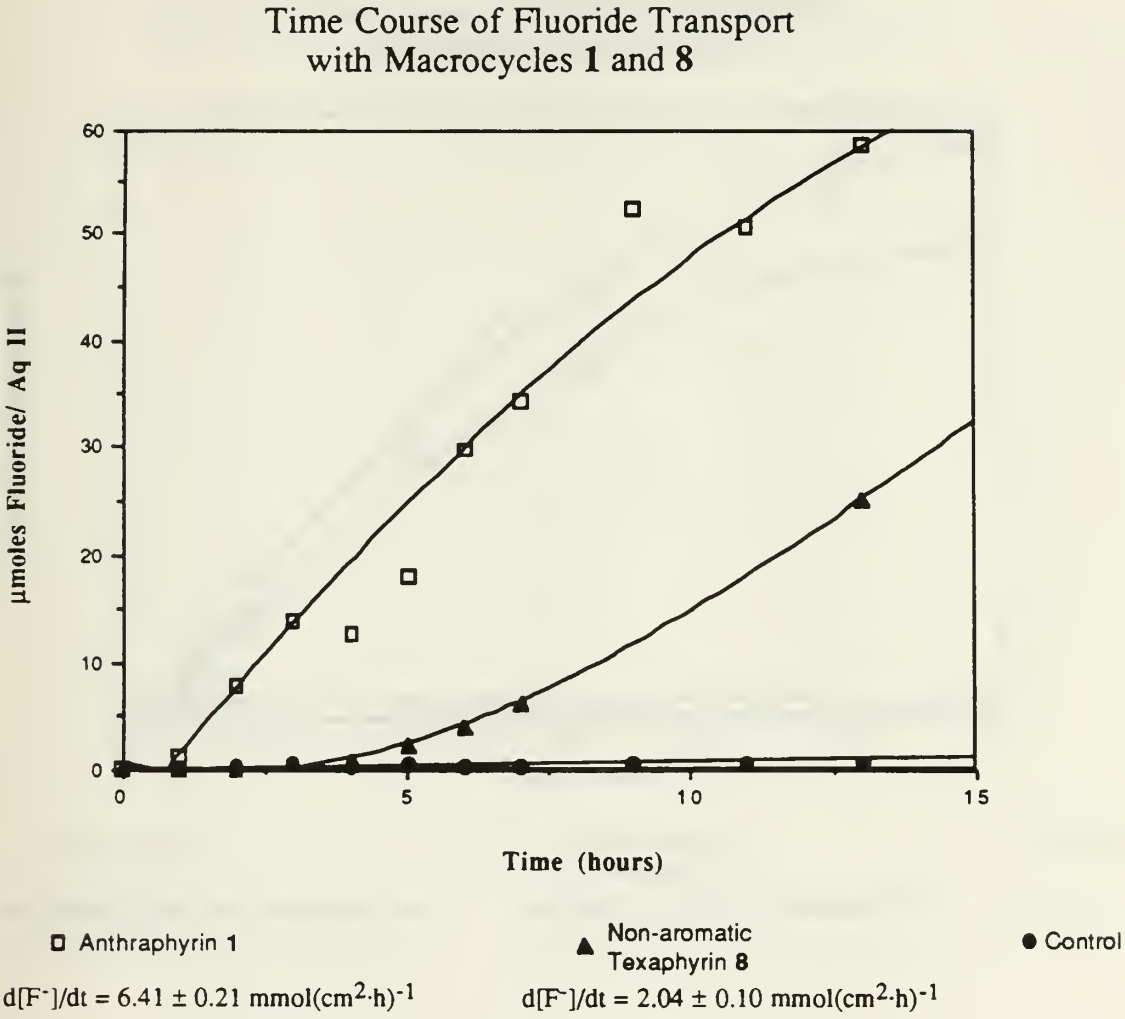
Supplementary Material

For

A Non-aromatic Anthracene Derived "Expanded Porphyrin": An Unexpected Anion Binding Agent.

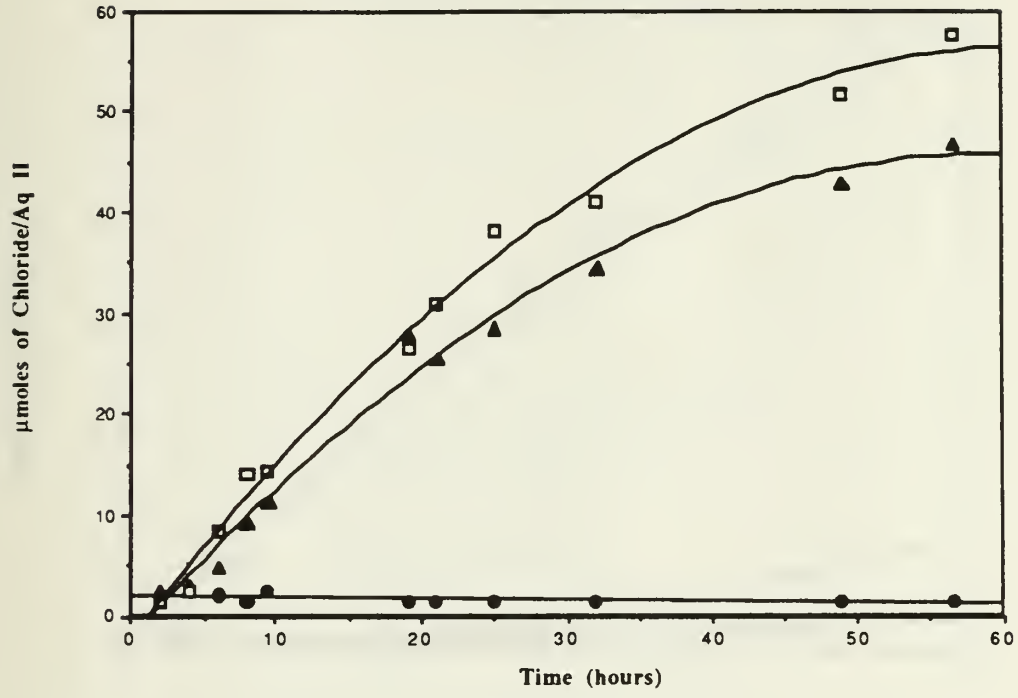
Jonathan L. Sessler,* Tarak D. Mody, Debra A. Ford, and Vincent Lynch

Department of Chemistry and Biochemistry, University of Texas, Austin, Texas 78712



Supplementary Figure 1. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.5M HF, adjusted to pH 3.2 with NaOH. Membrane; carrier: 1.0 mM, 10 mL CH_2Cl_2. Aq II(1mL); NaOH (pH 12). The release of fluoride anion into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiment was performed in the absence of carrier.

Time Course of Chloride Transport
with Macrocycles **1** and **8**



□ Anthraphyrin **1**

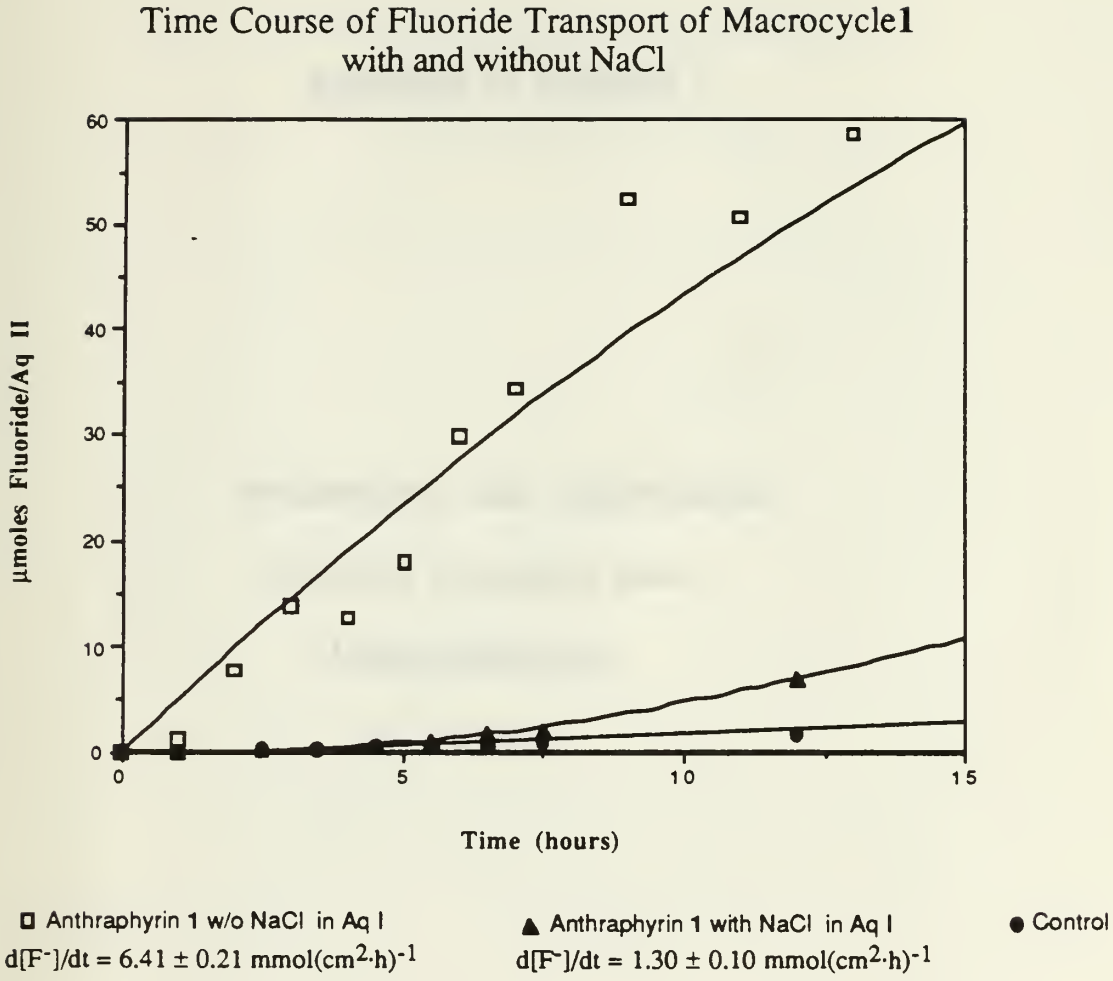
$d[Cl^-]/dt = 1.98 \pm 0.21$ mmol$(cm^2 \cdot h)^{-1}$

▲ Non-aromatic Texaphyrin **8**

$d[Cl^-]/dt = 1.44 \pm 0.21$ mmol$(cm^2 \cdot h)^{-1}$

● Control

Supplementary Figure 2. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.1M HCl + 0.4M NaCl (pH 1.2). Membrane; carrier: 1.0 mM, 10 mL CH_2Cl_2. Aq II(1mL); NaOH (pH 12). The release of Cl^- into the receiving phase, Aq II, was monitored at various times by a chloride combination electrode (Orion). In all cases, the control experiment was performed in the absence of carrier.



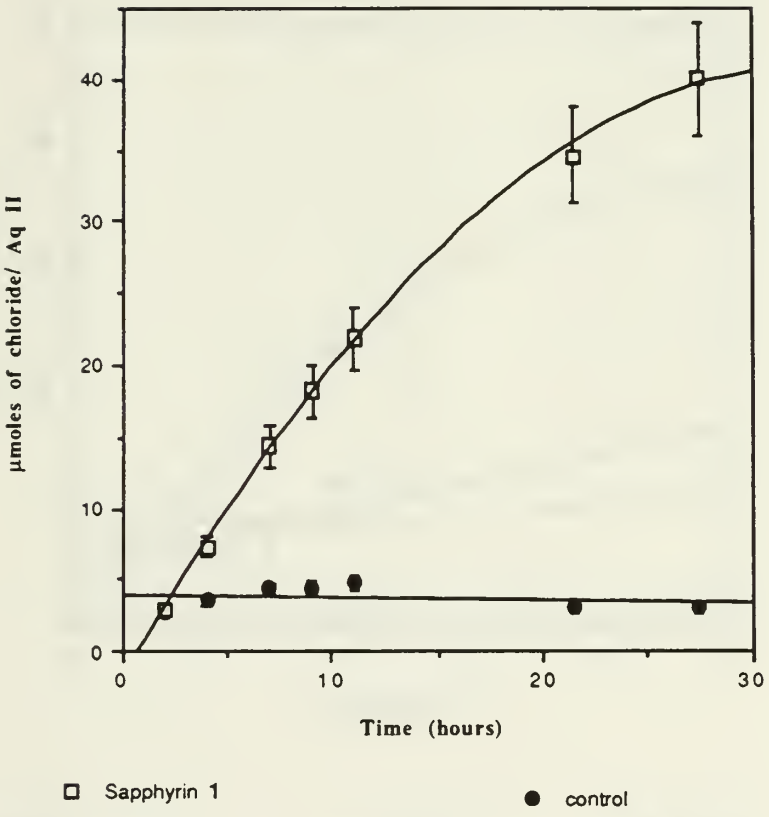
Supplementary Figure 3. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.5M HF + 0.5M NaCl (pH 3.2). Membrane; carrier: 1.0 mM, 10 mL CH_2Cl_2. Aq II(1ml); NaOH (pH 12). The release of fluoride into the receiving phase, Aq II, was monitored at various times by a fluoride combination electrode (Orion). In all cases, the control experiment was performed in the absence of carrier.

Appendix to Chapter 3

Preliminary and Unpublished Chloride Transport Data Using Sapphyrin As Carrier

Time Course of Chloride Transport
with Macrocycle **1**

(Preliminary Results)



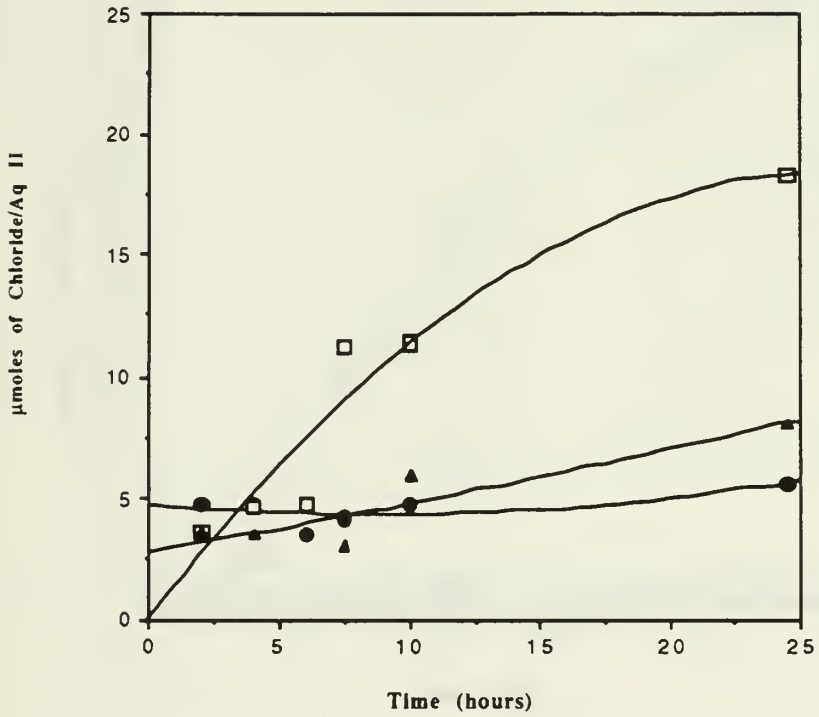
$d[Cl^-]/dt$ = 2.37± .23 µmoles/h

$d[Cl^-]/dt$ = 0 µmoles/h

Appendix A. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.1M HCl + 0.4M NaCl (pH 1.2). Membrane; carrier(10 mL): 1.0 mM in CH_2Cl_2. Aq II(1mL); NaOH (pH 12). The release of chloride anion into the receiving phase, Aq II, was monitored at various times by a chloride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier. Error estimated within ± 10%.

Time Course of ChlorideTransport
with Macrocycles **1** and **2**

(Preliminary Results)



□ Sapphyrin 1 d[Cl⁻]/dt = .655 µmol/h

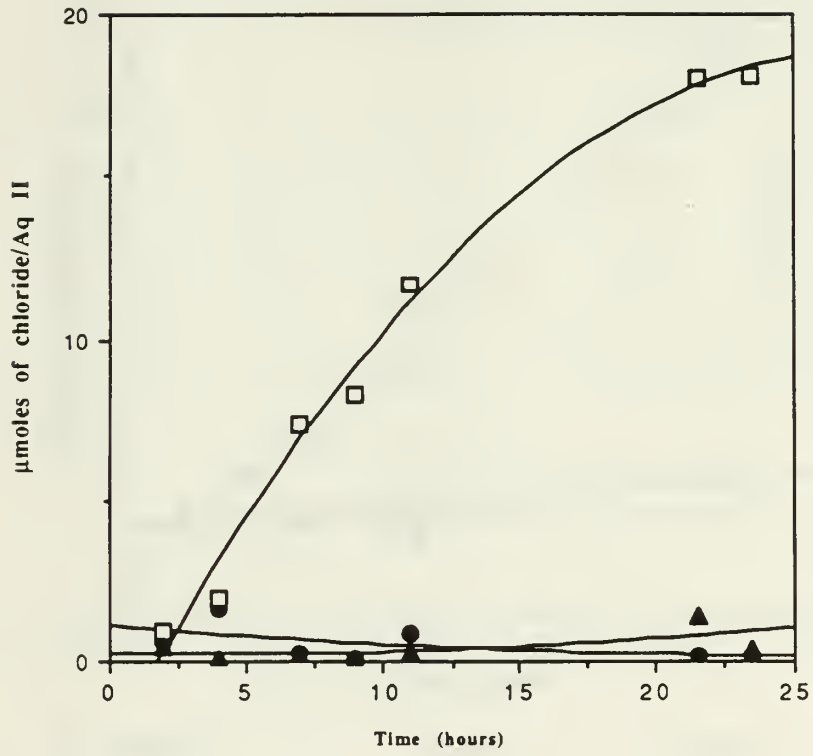
▲ OEP2 d[Cl⁻]/dt = .205 µmol/h

● Control d[Cl⁻]/dt = 0 µmol/h

Appendix B. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.25 M NaCl, buffered to pH 3.0 with acetic acid and sodium acetate. Membrane (10ml); carrier: 1.0 mM in CH_2Cl_2. Aq II(1mL); Acetic acid buffer (pH 3.0). The release of chloride anion into the receiving phase, Aq II, was monitored at various times by a chloride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.

Time Course of Chloride Transport
with Macrocycles **1** and **2**

(Preliminary Results)



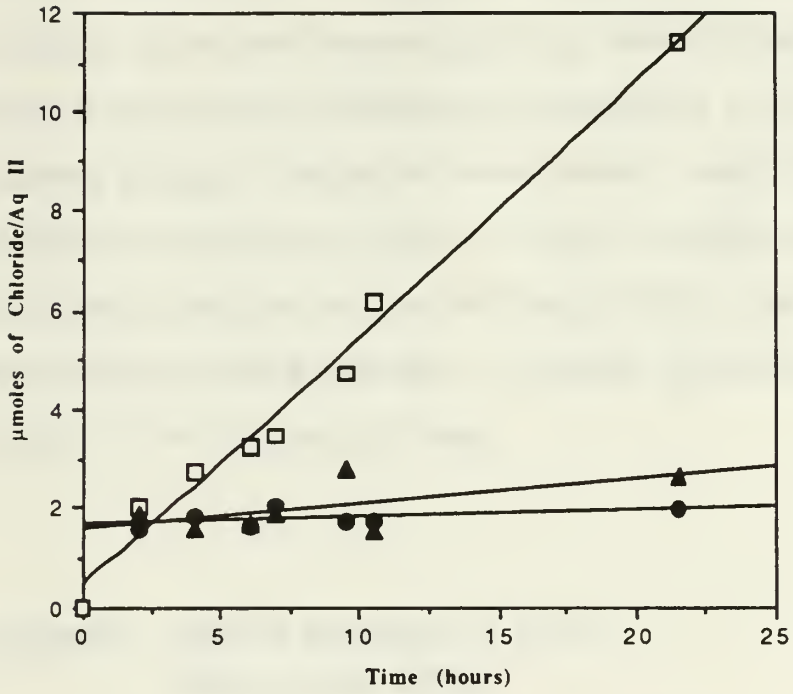
□ Sapphyrin **1** ▲ OEP **2** ● Control

d[Cl^-]/dt = 1.22 µmol/h d[Cl^-]/dt = 0 µmol/h d[Cl^-]/dt = 0 µmol/h

Appendix C. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq I (1mL); 0.25 M NaCl, buffered to pH 5.0 using acetic acid and sodium acetate. Membrane (10ml); carrier: 1.0 mM in CH_2Cl_2. Aq II (1mL); Acetic acid buffer (pH 5.0). The release of chloride anion into the receiving phase, Aq II, was monitored at various times by a chloride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.

Time Course of Chloride Transport
with Macrocycles **1** and **2**

(Preliminary Results)



d[Cl⁻]/dt =.483 µmol/h d[Cl⁻]/dt = 0 µmol/h d[Cl⁻]/dt = 0 µmol/h

Appendix D. Transport experiments were performed using a glass U-tube at 28°C. Conditions: Aq. I (1mL); 0.25 M NaCl, buffered to pH 7.0 using tris(hydroxymethyl) aminomethane-maleate. Membrane (10ml); carrier: 1.0 mM in CH_2Cl_2. Aq. II (1mL); Tris-maleate buffer (pH 7.0). The release of chloride anion into the receiving phase, Aq. II, was monitored at various times by a chloride combination electrode (Orion). In all cases, the control experiments were performed in the absence of carrier.

VITA

Debra Ann Ford was born in Memphis, Tennessee, on May 30, 1960, the daughter of Lillie B. Carter and Clarence Earl Ford. After completing her work at McKeesport Area High School, McKeesport, Pennsylvania, in 1978, she entered Allegheny College in Meadville, Pennsylvania. Several years later, she transferred to the University of Arizona in Tucson, Arizona, where she received the degree of Bachelor of Science in May, 1983. A year later, she was commissioned into the United States Navy. In August, 1989, she entered The Graduate School of The University of Texas.

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This thesis was typed by Debra A. Ford

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